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# ARCHIVES OF SURGERY

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## Foreword to Article by Dr. Arce

Nearly forty years have passed since the day in 1903 when Dr. Jose Arce received his first formal honor, the gold medal awarded by the Medical School of the University of Buenos Aires to its best student. The surgical world is well aware how thoroughly the promise of those early years has been fulfilled. Dr. Arce's distinguished achievements as surgeon, teacher, university administrator, author, editor and both provincial and national deputy have been recognized by many medical societies, universities and national governments of both hemispheres. For more than twenty years he has occupied the important chair of professor of surgery at his alma mater.

In accordance with the desire of the editors of the ARCHIVES OF SURGERY to place before their readers the most authoritative surgical thought of the day, the Chairman of the Editorial Board requested Dr. Arce to contribute to the pages of the ARCHIVES. He graciously consented, and the editors, therefore, have the privilege of publishing in this issue the first of two articles on the same subject as Dr. Arce's widely heralded exhibit prepared for the Eleventh Congress of the International Society of Surgery, held in Brussels in 1938, namely, echinococcosis.

EDITORIAL BOARD.

## HYDATID DISEASE (HYDATIDOSIS)

### PATHOLOGY AND TREATMENT

JOSE ARCE, M.D.

Professor of Surgery and Director of the Surgical Institute,  
University of Buenos Aires  
BUENOS AIRES, ARGENTINA

The disease caused by the development of one or more larvae of *Echinococcus granulosus* (Göze, 1782) in some part of the human body is usually known as hydatid disease, and its pathologic manifestation, the cystic tumor, as hydatid cyst. Strictly speaking, the first name is inappropriate, because the spread of the taenia's embryos does not always give rise to cysts. The correct name, therefore, is echinococcosis. This term was put forward some time ago, but in spite of its accuracy it is seldom used. On the other hand, in human beings the disease generally discloses itself by means of a cyst.

Hence, to my mind, the name hydatid disease as used in English-speaking countries should be replaced by hydatidosis. As to the term hydatid cyst, it may be applied to all localized forms of the disease except the osseous, in which cysts are not formed, for reasons to be shown later.

The aim of this paper is to offer physicians in the United States a brief summary of the actual knowledge of this disease, its pathologic features, its diagnosis and its treatment.

#### BIOLOGY OF THE PARASITE

*Taenia echinococcus* lives in the small intestine of the dog. This worm requires an intermediate host for reproduction, which it inhabits in the shape of larvae; these larvae, when swallowed by the dog, give rise to the formation of the taenia. The dog is, therefore, the definite host of the parasite.

There are many intermediate hosts, several of which are herbivorous, carnivorous or omnivorous mammals. Among the first, the most frequent are the bovines and ovines; among the omnivorous, man and the pig. Human infestation is easily explained by the fact that dogs live in close contact with man and the aforementioned animals. The carrier dog eliminates in his stools taenia rings full of ova, each of which contains a hexacanth embryo. The ova are deposited on grass, vegetables or stagnant water, where oxen, cows and sheep swallow them; thus the larvae find their way to the viscera, where they develop. The pig may become infested in the same way, although it is more likely to acquire infection through its coprophagous habits; this circumstance explains why it is infested in a higher proportion than bovines and ovines and supplies the reason for frequent mass infections in this animal.

Man becomes infested by use of vegetables and of water from brooks, ponds or lakes which have been fouled by dogs' stools. The parasites may be acquired even more directly, through having parasite-infested dogs as pets; and this is no doubt the most common way, particularly with children. Clinical observations have shown that children are more apt to acquire this disease than are adults because, like young animals, they are better ground for the development of the larvae.

Once the ova of *Taenia echinococcus* are in the first portion of the small intestine, the alkaline mediums there set free the hexacanth embryo. This immediately attaches itself to the villi, which it actively penetrates, thus reaching the capillary vessels of the portal system. The blood stream carries it to the liver, where it reaches a hepatic lobule, its first filter.

If it cannot pass through this barrier, the embryo settles there and starts to grow into what is called the larvated condition of the taenia.

This new appearance consists of vacuolation of the embryo until it is turned into a small vesicle full of fluid (fig. 1); the embryonic elements are pushed toward the periphery, surrounding the fluid and becoming what is known as the "germinative membrane" (fig. 1 *A*), outside which, and in close contact with which, is the "cuticular membrane" (fig. 1 *B*). The growth of this fluid-containing vesicle is indeed slow;

eventually it will become the "hydatid." Through its slow and progressive increase in size the larva causes a reaction on the part of the host, which tries to isolate it with a layer of connective tissue, the "adventitia" (fig. 1 *C*). The "hydatid" surrounded by the adventitia is usually called the "hydatid cyst."

But from the first stages in the hydatid's development the germinative membrane emits a growth which protrudes in the vesicle's cavity. Such



Fig. 1.—*A*, germinative membrane; *B*, cuticular membrane; *C*, adventitia; *D*, proliferative vesicle; *E*, scolices; *F*, "hydatid sand."

growths carry in their centers some elements of the cuticular membrane, which end by detaching themselves from it on being strangled by the cells of the germinative membrane. The result of this is the formation of small globular bags attached to the germinative membrane by a thin pedicle, similar in shape to the hydatid vesicle and with exactly the same elements, only in an inverted position, i. e., those of the germinative membrane are outside and those of the cuticular membrane inside. These globular corpuscles are called "proliferative vesicles" (fig. 1 *D*).



The process repeats itself inside each of the proliferative vesicles, but this time the growths are directed outward, so that their central zone remains in communication with the vesicle's cavity. In a later stage of evolution hooks and suction apparatus appear in the free end of each of these growths as means of fixation. Finally, these ends become invaginated in such fashion as to protrude in the cavity of the proliferative vesicle. These growths, armed with hooks and suction apparatus, are the "scolices" (fig. 1 *E*).

The scolices protrude more and more in the cavity until only a very thin stalk remains, attaching them to the wall of the proliferative vesicle where they originated. As the walls of the proliferative vesicles become progressively thinner, they finally break, and the scolices are left free in the fluid of the hydatid vesicles. The law of gravity and their greater density make them fall to the bottom of the vesicle, where their accumulation resembles that of grains of sand; owing to that similarity, Dévé called this conglomeration "hydatid sand" (fig. 1 *F*).

This is, in short, the description of the development of the larvae. Two things may subsequently happen to them.

1. Suppose that they have developed in some organ of a sheep or a cow (animals commonly used as man's food) and that on slaughter of the animal these organs were not destroyed. On country estates and even in small villages where no slaughterhouses exist and no sanitary precautions are taken during this process, dogs are generally fed with the viscera of these animals. This is how the scolices find their way to the small intestine; once in the villi, they attach themselves by their suction devices. Each of these scolices becomes a *Taenia echinococcus* capable of producing ova which will eventually give origin to the larvae just described. And so the cycle starts once again. The dog, is, therefore, the definite host of *Taenia echinococcus*; the sheep, the cow and the pig are the intermediate hosts. If the latter were to disappear, and with them the parasite-infected viscera, the cycle would be interrupted and a great number of larvae would never attain the adult stage of *Taenia echinococcus*. This is what actually happens in man.

2. Suppose instead that the larvae have developed in some viscus of the human body (liver, lung, etc.), where hydatid cysts have been formed. Since dogs never feed on human remains, these larvae are, naturally, lost for reproduction of the parasite. In short, the evolution of the taenia is interrupted before its completion.

#### PROPHYLAXIS

From the facts just stated, important conclusions concerning prophylaxis can be drawn. Unfortunately, these have not yet been included in the health legislations of some countries affected by this disease, such as Argentina. The fight against echinococcosis requires:

1. The destruction of the viscera of parasite-infested animals, the taenia's intermediate hosts, especially those commonly used by man as food and therefore in close contact with dogs, to render inactive the menace of the larvae.

2. Compulsory treatment of infested dogs with arecaline, which efficiently and surely will exterminate the taeniae.

With these two measures taken, the taenia formation (*Echinococcus granulosus*) and the larvae formations (hydatid cysts) would be prevented. Thus, hydatidosis, a plague affecting man and some useful animals, could be held under control or totally eradicated, as it has been in Iceland.

#### THE LARVAE OF ECHINOCOCCUS GRANULOSUS IN THE HUMAN SYSTEM

Once in the blood stream and through the portal vein, embryos of *Taenia echinococcus* reach the capillaries of the liver, where they are met with a true filter before passing on to the suprahepatic veins and to the inferior vena cava. Those which manage to go through this filter arrive at the right side of the heart and pass through the pulmonary arteries to both lungs, where the blood stream becomes slower in the huge capillary network where hematosis is carried out.

Back in the left side of the heart through the pulmonary veins, they reach the aorta; this vessel places them on the road to every organ of the human body. Any artery can then carry them to the terminal capillaries, where they can produce an embolism and so fix themselves and develop into hydatid vesicles.

In cases of mass infestation several embryos develop at the same time and give rise to vesicle formation. The typical example of this is to be found in the pig—an animal of coprophagous habits—and sometimes in the sheep. In the cow this does not happen so often, perhaps owing to the marked difference in feeding habits.

Mass infestations are not frequent in man; however, from time to time patients have been seen with hydatid cysts in more than one organ or with several cysts in one organ. This seems to be the result of a multiple infection, either in one stage or in successive ones.

A careful study of the proportion in which different organs are affected by this disease shows that the liver stands first; then the lungs, and finally other viscera in approximately equal numbers.

These differences are easily explained by the route followed by the embryo from the intestinal villi to the arterial tree. In fact, both the liver and the lungs are filters that lie in the pathway, and it is in their capillaries, especially those of the liver, that the embryos find favorable conditions for settling themselves and developing. But if they have

succeeded in reaching the arterial stream they can stop in any capillary ending, such as those of the brain, the spleen, a bone or the connective tissue. This explains why the localization in different organs—except, of course, the liver and the lungs—is proportionally even.

In figures these localizations can be described as follows: of, say, 100 hexacanth embryos reaching the portal vein, 70 remain in the liver, 15 in the lungs, 4 in the muscles and 2 in the spleen, kidneys, brain and connective tissue (fig. 2).

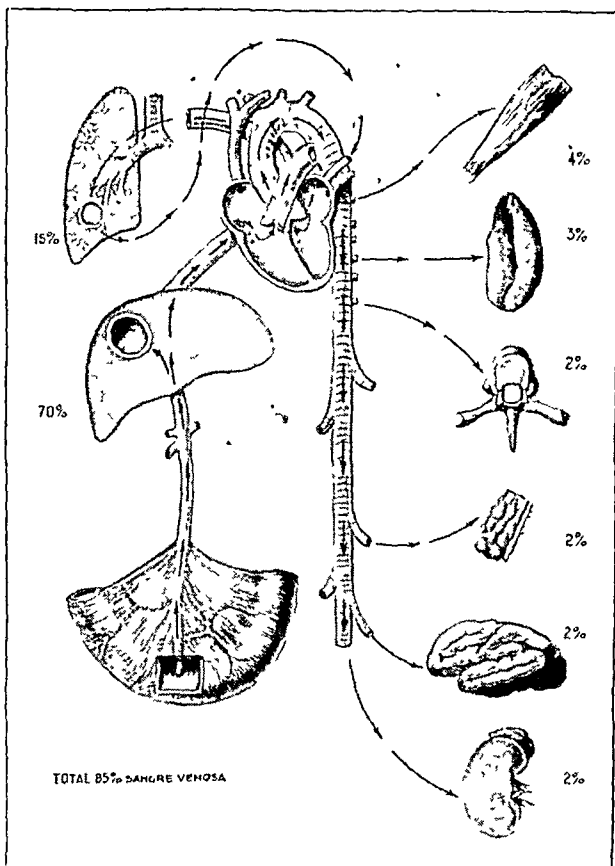


Fig. 2.—Distribution of hydatid cysts in the organs of the human body

#### HYDATID CYSTS

The development of the hydatid vesicle gives rise to a reaction of the host tissues which surround it; this reaction takes the shape of a membrane called the adventitia. The hydatid vesicle with its two enveloping membranes, the cuticular and the germinative, its contents and the adventitia form a cystic tumor bearing the name hydatid cyst.

It is obvious that the histologic texture of the adventitia, although similar in all cases, varies according to the organ infested. Hence

the difference in some phenomena and complications of this disease which, in some cysts of the liver and of the lungs, mark their anatomic and clinical features. I shall describe first the general texture of the adventitia and later the differences found in cysts of the liver and cysts of the lung.

The adventitia surrounds, but is never linked in any way to, the hydatid vesicle; they are only in intimate contact. This explains why in some cases, once the adventitia has been opened, the vesicle can be easily extracted. This true "hydatid birth" may be used as a therapeutic measure, but through rupture of the adventitia it may also occur spontaneously and originate secondary hydatidosis by transplantation. I shall deal with this possibility later.

Two factors govern the histologic process of formation of the adventitia: (*a*) the reaction of the cells of the containing organ to the foreign body and (*b*) the influence of the eccentric pressure caused by the parasite's growth on those cells. It must be borne in mind that the larva is nothing but a living foreign body.

In the adventitia, microscopic examination shows different structures, according to the parasite's age. The first stages can be studied only experimentally. In short: The adventitia is formed by three layers, and these become modified as the parasite grows older. The inner layer, in close contact with the cuticular membrane of the larva, consists of young elements of connective tissue bordered on the outside by a white cell infiltration. The middle layer consists of an abundant plasma cell and lymphocytic infiltration. Finally, the outermost structure—the outer layer—is formed by cells of the affected organ, divided into two zones: the inner (nearer the middle layer), of cells showing signs of turbid degeneration, and the outer, of cells progressively undistinguishable from those of the cyst-containing organ.

When the parasite's size is such that it manifests itself clinically by the presence of a tumor, the adventitia undergoes alterations caused by this outward growth. Capillaries and other small vessels become obliterated, and the resulting lack of blood supply gives rise to ischemic necrosis, to fibrous changes or to hyaline degeneration. The result of this necrosis is a structureless magma of a caseous type, which is frequently the first step to the partial or total calcification of the adventitia.

In old, uncalcified cysts the adventitia has an inner layer with necrotic processes and a middle layer of connective tissue with hyaline degeneration; the outer one is of a reactive type with histiocytic and lymphocytic infiltration and a structure which slowly becomes undistinguishable from the cells of the parasite-infested organ.

In organs poor in connective tissue, such as the brain, or in those in which this tissue becomes highly differentiated, thus possessing small reactive power, the adventitia is notably scarce.

I have already spoken of the other constituents of the hydatid cyst, the hydatid vesicle with its two membranes—cuticular and germinative—and the hydatid fluid. The fluid is crystalline and, like the membranes, always germ free.

The hydatid fluid contains proliferative vesicles and scolices; cysts without them are called *acephalocysts*, or, from the biologic point of view, sterile cysts.

Inside the main hydatid vesicle, or mother vesicle, a fully developed daughter vesicle may be found. These daughter vesicles are of a similar structure to that of the main vesicle, with an outer cuticular layer, an inner germinative layer and a fluid content. As a rule, they are sterile, i. e., without scolices and proliferative vesicles, although cases have been recorded in which these elements were present. The most generally accepted theory nowadays on the formation of these daughter vesicles is that they appear as results of some mechanical, toxic or infectious action on the larva, i. e., the mother vesicle. In other words, the daughter vesicle is nothing but a reactive defense on the part of the parasite.

The fact that both the hydatid fluid and the membranes are germ free is the foundation for the treatment of sterile cysts by extraction of the parasite and suture of the adventitial incision without leaving a drain (Posades' method).

But things are not always as I have just described them. I have spoken only of the simple hydatid cyst, which may become a complicated cyst through (*a*) mechanical or (*b*) infectious factors. The former (traumatism) may cause a fissure, a tear or a full rupture of the parasite's membranes and even of the adventitia; these phenomena may precede either partial or total evacuation to the exterior of all or part of the larvae resident in certain organs (cyst opened in a bronchus, in the intestine, in the bile ducts, in the renal pelvis, etc.) or the emptying of the cysts into a cavity, such as the peritoneum (peripheral cysts of the liver opened in the peritoneal cavity).

The infectious factors (germs) may give rise to pericystitis at the level of the adventitia and cause the death of the hydatid vesicle by altering its membranes and their contents. This is the most frequent complication in a simple hydatid cyst, which therefore becomes an infected or septic hydatid cyst. This name is not quite appropriate, as the only part of the cyst which becomes infected and septic is the adventitia; when this happens, the elements contained within this membrane die and disintegrate. Thus the cyst is turned into a cavity full of all sorts of debris—fragments of membranes, daughter vesicles, necrosed tissues, pus, bile, urine, mucus, etc., according to the individual circumstances. The hydatid fluid seems to be an excellent medium for the germs' development. With regard to the wall of this septic cavity, i. e., the adventitia, it is the site of a more or less important septic process.

Septic cysts should not be mistaken for dead cysts. The latter have become disintegrated, and the hydatid vesicle has either undergone gelatinous degeneration or has turned into a "mastic" similar to tuberculous caseum. In these circumstances the parasite's death is due to unknown factors or to factors difficult to determine, such as a lack of vital energy on the part of the original embryo or accidental or surgical trauma.

A septic infection of the cyst is usually favored by a tear in the membranes, and it takes place either through contamination coming from the already infected adventitia or by germs which increase their virulence on arriving in the vesicle's contents.

*Hydatid Cysts of the Liver.*—The slow growth of the hydatid vesicles in the liver, together with the organ's reaction to the parasite (their adventitia) prevents the larvae from coming into contact with the intra-hepatic bile ducts. But sometimes, owing to unknown reasons, this contact may actually take place, either because of the decrease in the neighboring defense reaction or because the adventitia totally surrounds an important duct which cannot be obstructed and annulled. Whatever the reason, the fact is that a duct may happen to come into contact with the inner surface of the adventitia, and then, through partial necrosis, the bile floods the cyst, interrupting the contact of the larva and its host and causing the former to suffer. This suffering can vary from the production of daughter vesicles to the parasite's death with disintegration of the membrane and mixture of its contents with bile. The bile may carry the infection or favor it when germs develop in the adventitia. Finally, the cyst's contents may be evacuated into a duct of a certain size and through it to the exterior. As a result of these phenomena, cysts of the liver may cause obstruction, angiocholitis or both complications at the same time. That these processes are slow and of variable intensity is clearly shown clinically. It is known that besides the severe complications just mentioned there are: (a) clean (aseptic) cysts, with hardly any traces of bile, which are cured without drainage; (b) aseptic cysts with a greater bile content, which occur in several points of the adventitia and require drainage, and (c) septic cysts with a large bile content (true cholehydatid abscesses) requiring *sine qua non* marsupialization (this is an ample drainage of the pouch formed by the adventitia, which thus becomes like the marsupial's pouch).

According to their localization, hydatid cysts of the liver may be central or peripheral, and the latter may be of thoracic or of abdominal evolution. When a complicated cyst shows a definite thoracic direction, its adventitia generally pursues the following course: it emerges from the organ, adheres to the diaphragm and causes a pleural adhesion and then a process of pulmonary condensation *in situ*. Finally the cyst tries to break through all these adhesions so as to find a way out at the

expense of destruction of a bronchial wall. The ultimate stage is the expulsion of the cyst's contents through the air passages; in the expelled matter altered parasitic elements, bile and pus are usually found.

When peripheral cysts with an abdominal evolution arrive at the surface of the organ where they are situated and thus at the peritoneal cavity they are easier for the surgeon to reach, but at the same time they become more exposed to trauma and to rupture of the adventitia. If such accidents take place, the contents fall into the peritoneal serous membrane (hydatidoperitoneum) and may give rise to secondary echinococcosis. This rupture may be spontaneous or, what is practically the same thing, may occur through a slight trauma unperceived by the patient. The spontaneous rupture is due to the growing larva's eccentric pressure on an adventitia unprotected by any organic tissue.

It has already been said that the larva's growth causes ischemic degeneration through pressure and obliteration of the adventitia's capillaries and other small vessels. But when a large vein is affected this process of thrombosis obliterans may not take place; instead, when the vein's wall comes into contact with the hydatid vesicle, a communication appears between the two by a process of corrosion. As a result of this the scolices reach the main blood stream, arriving first in the lungs and later in any organ of the body. This spread may cause embolisms capable of developing into new hydatid cysts; it is secondary metastatic echinococcosis.

*Hydatid Cysts of the Lung.*—The larvae which settle and develop in the lung in their eccentric growth have to deal not with a thick parenchyma, as in the liver, but with a less dense tissue subject to physiologic changes affecting the adventitia's formation and the parasite's evolution. The true adventitia is slighter than that of the liver; its thicker appearance is due to the fact that a certain strip of lung tissue surrounding the tumor remains normal, without taking any active part in the respiratory movements. This strip, on account of its appearance, has been called the second adventitial zone, or false adventitia. It is nothing but a peritumoral zone of atelectasia which surrounds the entire hydatid cyst (larva and real adventitia) and isolates it from the normal tissue, thus diminishing future interference with the cyst by the movements of breathing. The explanation of such interference is as follows: As the cyst increases in size, the smallest neighboring bronchial branches are repelled and crushed and many of them even obliterated. But at one stage the tumor may come into contact with one or more small bronchi the walls of which resist the cyst's expansion in such fashion that they end by meeting the outer aspect of the quitinose membrane. This also happens in the liver when the large ducts are enveloped by the adventitia, but, owing to their histologic and functional characteristics, the small bronchi are much more resistant to these outward growths. When

this takes place it may be stated truthfully that at points of contact between the tumor and the bronchi the weak adventitia of pulmonary cysts is composed only, or almost only, of the bronchus. But as the larva continues to grow, it keeps on pressing against the wall of the bronchus until this structure is worn off and finally becomes perforated.

From this moment the outer aspect of the larva is directly in contact with the lumen of one or more small bronchi (fig. 3 *A*). Through a deep inspiration, aided perhaps by a fit of coughing, some air penetrates between the adventitia and the quitinose membrane, which, as I have already stated are closely related without being connected in any way.

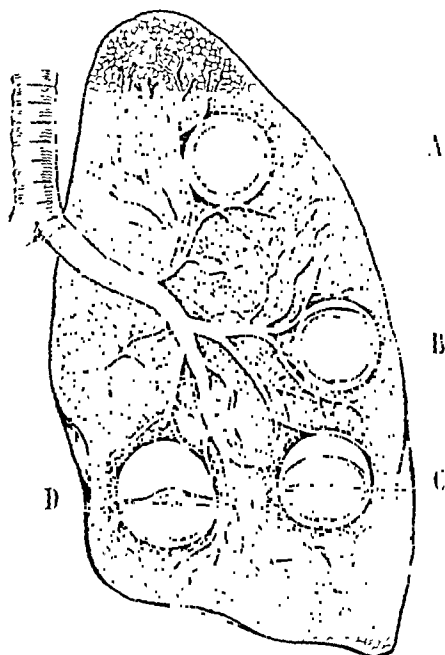


Fig. 3.—Hydatid cysts of the lung. See text for explanation.

The worn-out edge of a bronchial cartilage or even mere effort on the part of the bearer may cause a tiny fissure in the membrane and thus a loss of hydatid fluid. The presence of this fluid on the surface of the bronchial epithelium gives rise to renewed fits of coughing followed by further deep inspirations. Hence more air penetrates between the larval walls and the adventitia until it becomes what has been called pneumoperivesiculum (fig. 3 *B*).

At a later stage, and undoubtedly assisted by a widening of the original tear in the parasite's membranes, air slips into the cavity where the expelled hydatid fluid formerly was contained. In this way two air chambers are found, one intravesicular and another perivesicular, separated by the echinococcus membranes (fig. 3 *C*).



If the hydatid fluid has not been totally evacuated from the cavity and a small amount still remains, the membranes—or part of them—float on it like a “camalote” on water; the rest of the cavity is full of air (fig. 3 D). This peculiarity is present especially in cases of death and disintegration of the parasite or of septic infection of the cyst. The membranes, or what is left of them, float in a more or less purulent fluid.

Finally, during a fit of coughing the patient may expel hydatid fluid and all the parasite's membranes (hydatophthisis or hydatid vomica) through a breach in some bronchus. In some cases, particularly if the cysts are small, this causes spontaneous healing of the disease. In other instances the vomica is composed only of hydatid fluid; if this is the case the membranes remain imprisoned within the adventitia and may later give rise to a false abscess of hydatid origin and even to peritumoral complications.

#### SYMPTOMS

Hydatidosis manifests itself through two kinds of symptoms: those common to all affected organs and those specific to any given organ. I shall deal in this paper only with the former, together with the specific symptoms of cysts of the liver and of the lungs, which constitute four fifths of hydatid cysts of the human body.

Hydatid cysts can be divided into simple and complicated cysts. Simple hydatid cysts are those in which the parasite is alive and the adventitia intact. In the complicated cysts the adventitia, the parasite or both have undergone certain changes. The adventitia may break, become septic or even become calcified. The parasite may die, its membranes and other elements becoming disintegrated and blood, air, bile or pus, mixed with hydatid fluid and remains of membranes, being found in the hydatid cavity.

*Simple Hydatid Cysts.*—Symptoms common to all these cysts are: (a) the hydatid tumor and (b) the blood and serologic manifestations which together constitute the biologic syndrome. The tumor is the result of the hydatid vesicle's growth, and the biologic syndrome is the display of the reactional interchange between the parasite and its hosts.

*Hydatid Tumor.*—The hydatid cyst is of slow growth. Unless it is situated superficially and therefore easily available to inspection and palpation, there is no clinical evidence of the cyst. Cysts which are recognizable early are those of the subcutaneous cellular tissue, of scars from operations for hydatid cysts (secondary hydatidosis), of the muscles, of the salivary glands or of the thyroid. Cysts of the brain in adults do not become clinically conspicuous until the cranial hypertension is detected by a nerve specialist, but in children they can be diagnosed through a parchment sensation due to a softening of the

cranial bones. As for cysts of the lungs, they are often discovered only when, for some reason or other, a physician has a roentgenogram taken or a roentgenoscopic examination is performed.

The hydatid tumor is usually single. When it can be seen and palpated, it shows a more or less spheroid or ovoid shape. But as in most cases it only partially emerges from the containing organ, only a segment of the sphere can be seen or felt; the rest of the tumor is embedded in the organ's parenchyma.

The tumor is generally smooth, with fluid at a certain tension and dull to percussion. In exceptional cases a special thrill can be felt; this is the hydatid thrill.

If the tapping is done on one finger applied to the tumor, the vibration may be felt in it, though sometimes in order to find it it is necessary to hold the second, third and fourth fingers slightly separated, in which case the second and the fourth perceive the thrill brought about by percussion on the third. If the unknown physical conditions which cause this phenomenon could be reproduced elsewhere, there is no reason why this thrill could not be found with other fluid tumors, but in my long practice I have never come across it anywhere else. That is why I can firmly state that the hydatid thrill is specific for cysts caused by echinococci.

A simple hydatid cyst, even after many years, does not noticeably affect the carrier's general condition, and it is painless. Often the patient with a hydatid cyst in the abdomen discovers it by mere chance.

*Biologic Syndrome.*—Though the hydatid vesicle is isolated by the adventitia from the human system at the point where the host—at whose expense the parasite lives—absorbs metabolic products, it is in this process of absorption that the larvae affect the tissues and the body fluid, and one must seek in this process the explanation of the biologic syndrome.

A triad characterizes this syndrome: (*a*) eosinophilia; (*b*) a positive reaction to Imaz-Lorentz's complement fixation test and (*c*) a positive reaction to Casoni's cutaneous test.

(*a*) Eosinophilia: It can be positively stated that there is eosinophilia only when the proportion of eosinophils in the blood is above 5 per cent. That is why I generally consider an eosinophil content of more than 5 per cent as suggestive of the presence of a hydatid cyst. But as a means of diagnosis the percentage of eosinophils is worthless if it is borne in mind that most forms of verminosis also produce an increase of these leukocytes; its real value resides in its association with one or both of the other two components of the biologic syndrome.

Eosinophilia is not a constant symptom of hydatidosis; in fact, it is one of the least of the three, and its absence should not lead one to discard the possibility of the existence of a hydatid cyst. My experi-

ence leads me to state that a high eosinophil count, in some cases reaching 70 per cent, has a diagnostic value only when its presence coincides with one or both of the other two components of the biologic triad, especially with the positive reaction to Casoni's test of the skin.

(b) Imaz-Lorentz Complement Fixation Test: This is based on the principle of the Wassermann test. The result is by no means constant; my experience has taught me that it is negative in 40 per cent of patients with hydatid cysts.

(c) Casoni's Test of the Skin: This is carried out by injection of 0.1 to 0.6 cc. sterile human, bovine or ovine hydatid fluid into the dermis of the forearm. If the patient has a hydatid cyst, a characteristic reaction appears at the site of injection in the form of an urticarial papule, the size of which varies between that of a dime and that of a quarter. It usually appears five to ten minutes after the injection (early reaction), and when the reaction is positive a more or less extensive edema, with redness of the skin, can be observed twenty-four hours later (late reaction).

This cutaneous test is the most reliable of the triad's components; my experience shows that it fails in only 10 per cent of cases. It is advisable to carry it out after the complement fixation test and the investigation of eosinophilia, as sometimes a small intradermal injection of hydatid fluid may increase the number of eosinophils and turn a negative Imaz-Lorentz reaction into a positive one.

*Complicated Hydatid Cysts.*—As I have already stated, the parasite may die or the adventitia become calcified. In either case, and especially if the cyst cannot be seen or felt, the patient may ignore it, owing to the usual disappearance of the biologic syndrome. In these circumstances the cyst becomes a foreign body and as such is isolated from the general system.

As for septic cysts, they cause the general and local symptoms common to all septic processes. In the ordinary cases there are a loss of appetite and a temperature up to 100 F., without any further repercussions on the patient's general condition. But sometimes the symptoms may grow more severe and even cause an acute infectious picture, with local reaction at the site of the tumor, a temperature between 100 and 102 F., adynamia, a subicteric tint, etc. Between these two conditions there are any number of intermediate stages.

#### DIAGNOSIS

As with all diseases of long and silent evolution, the diagnosis of hydatid cyst is not always easy. In countries with echinococcus-infected zones, the place where the patient lives is of the utmost importance in cases of doubt. If one is faced with a hepatic or abdominal tumor of silent evolution in a patient coming from a zone where hydatidosis is

endemic and if other signs do not point to the contrary, one must suspect a hydatid cyst. In that case one must not hesitate to have a roentgenogram taken and to carry out the three tests for the biologic syndrome.

In such countries as Argentina, a tumor which is smooth, more or less round, at a certain tension and associated with an unimpaired general condition should always be suspected of being a hydatid cyst; this is the true diagnosis in 80 to 90 per cent of cases. At any rate, in the presence of such a tumor one must investigate the concentration of eosinophils in the blood and carry out both the Imaz-Lorentz and the Casoni test. Even if the results are all negative, one must not altogether reject the diagnosis of hydatidosis, but if the result of any one of them, particularly the last mentioned, is positive, the diagnosis becomes certain. Owing to these circumstances I insist that the diagnosis of echinococcic cysts is a difficult matter, so much so that it is sometimes made only on the operating table.

#### TREATMENT

Medical treatment has so far failed; only surgical treatment has proved effective. Dead or alive, the parasite is a foreign body within the human system, and unless it is removed it may give rise to complications. Broadly speaking, the treatment of hydatid cysts lies in the removal of the parasite and in the appropriate handling of its isolating membrane, the adventitia. In the case of a single cyst it is a matter of reaching it by the shortest way and evacuating its contents, but if there are several of them, situated in one or more organs, the task becomes more complicated, and therefore it should be carried out with the utmost caution and care; one should deal first with the largest cysts or those which look most dangerous to the patient. Sometimes it is possible to evacuate two or more cysts in a single operation, but in most cases, after weighing certain circumstances, such as the patient's general condition and the cyst's localization, it is necessary to repeat the surgical procedure as many times as there are cysts.

In the evacuation of the parasite and the treatment of the adventitial pouch the surgeon is faced with certain problems. When the evacuation is performed in a cyst containing a living parasite, care should be taken to protect the operating field against the action of the hydatid fluid and its probably fertile contents (scolex, proliferative vesicles, etc.). Before the fluid and the membranes are removed, towels should be placed so as to cover every neighboring structure as well as the operative wound and any serous membrane which has had to be opened (peritoneum, pleura, etc.). After the total evacuation of the parasite (and provided the cyst-containing organ allows it) the adventitial pouch is sterilized either with ether or with a 2 per cent concentration of a 40 per cent solution of formaldehyde. It is claimed that all these precautions prevent the appearance of secondary hydatidosis (the development of new cysts through the spread of scolices or proliferative vesicles).

The treatment of the adventitial pouch depends on the features of the case, the localization and size of the cyst and whether the cyst is septic; on these considerations are based the different propounded technics—suture without drainage (Posadas); marsupialization and drainage, and total or partial resection of the pouch.

*Removal of the Parasite and Suture of the Pouch Without Drainage (Posadas' Technic).*—In 1895, an Argentine surgeon, Alejandro Posadas, basing his procedure on the fact that hydatid cysts are germ free, advocated the evacuation of the parasite followed by an appropriate treatment of the pouch and its suture, as well as of the wound, without drainage. Shortly afterward he published a brilliant statistical account of his procedure, which was first employed on cysts of the liver; later, in 1896, on those of the lung, and still later on those in other locations.

*Marsupialization and Drainage.*—Infected cysts cannot be dealt with by means of Posadas' method. The adventitia must be opened and the parasite—or what has been left of it by the infection—removed. Then, after a careful treatment of the cavity of the pouch, the edges are sutured to those of the operative wound. Thus a pouch opening on the skin has been created; owing to its similarity to the marsupial's baglike receptacle, this procedure has been called "marsupialization." Two or three drainage tubes should be placed in the cavity of the pouch.

As not all hydatid cysts are aseptic and as in any case the cysts run the risk of infection during or after the operation, some surgeons apply this marsupialization technic and drainage to the majority of cysts they operate on, whether they are infected or not.

The drained pouch heals by second intention; this process is a very long one, possibly lasting from thirty to forty-five days and even as much as a year and a half or more. A careful and detailed treatment of the pouch during the operation, so that all membranes, daughter vesicles or other foreign bodies are removed, is the only way of shortening this long period of recovery. Calcification of the adventitia is another factor which may delay for years the total healing of the wound.

*Removal of the Hydatid Cyst Together with the Adventitia.*—In some cases, owing to the small size of the cyst, its scanty connections or its favorable situation, the whole of it—the parasitic vesicle together with its contents and isolating adventitia—is removed during the operation. This procedure is applied particularly for hydatidosis of the omentum or of the peritoneum.

*Hydatid Birth.*—This is possible only with rare and protruding cysts, most of which are situated in the liver. Once the tumor has been reached, with avoidance of incision of the underlying parasite's membranes, the adventitia is cut; thanks to the lack of adhesions and the elasticity of the cuticular membrane, the whole hydatid vesicle emerges through the opening in the adventitia. Exceptionally an acci-

dental fissure in the adventitia may be widened and used for this hydatid birth. The operation is ended by suturing the resulting pouch and the operative wound without leaving a drain. When this exceptional technic is used there should be no fear of secondary hydatidosis, as any fertile contents which may be found in the vesicle (proliferous vesicles, scolices, etc.) will not come into contact with the patient's tissues.

#### DIFFERENT LOCALIZATIONS

I have already stated that cysts of the lung and liver together constitute 85 per cent of hydatid cysts in man. I intend to study some of the peculiar characteristics of the evolution, diagnosis and treatment of cysts in both locations and later to sketch those of the kidney, spleen and peritoneum, together with osseous hydatidosis.

# PERNICIOUS ANEMIA FOLLOWING TOTAL GASTRECTOMY

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Pernicious anemia following extensive surgical ablation of the stomach occurs with a frequency which bespeaks more than a coincidence. Since of recent years advances in surgical technic and changes in surgical philosophy have resulted in more radical resections of the stomach, pernicious anemia as a late complication is to be expected more often than heretofore. The excellent summaries by Goldhamer<sup>1</sup> and by Singer and Steigmann<sup>2</sup> had brought the number of reported cases up to 34 by 1934. Since that time about 20 additional cases<sup>3</sup> have been reported, illustrating essentially the same points stressed in the literature previously, i. e., that the symptoms and the typical hematologic picture develop in two to fifteen years (with the exception of 2 cases<sup>4</sup> in the entire series reviewed); that signs and symptoms of degeneration of the posterolateral column often accompany the anemia; that other features of the pernicious anemia syndrome, such as gastrointestinal symptoms, evidences of hemolytic anemia and, of course, achlorhydria, are almost always found; and finally, and perhaps most significantly, that the response to anti-pernicious-anemia therapy is specific and dramatic.

The case reported here illustrates the aforementioned points and in addition emphasizes the insidiousness of the onset, the necessity of long-

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From the Departments of Medicine and Surgery, the Cook County Hospital.

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4. Goldhamer.<sup>1</sup> Fleischhacker and Klima.<sup>3a</sup>

continued observation and the specificity of the response to liver therapy. We have had the good fortune to follow our patient, though somewhat intermittently, from the time of his gastric resection until the appearance of his pernicious anemia syndrome; in addition, we have been able to study his bone marrow both before and after therapy, an observation we believe to be unique in a case of this type. Unfortunately his cure was of short duration; four months after his discharge from the hospital he committed suicide by drinking saponated solution of cresol.

#### REPORT OF A CASE

At the time of his first admission to the Cook County Hospital (October 1933) the patient was 33 years old. He was American born, of Austrian extraction. He was a mechanic. He had been well till five or six years previously, when abdominal distress with severe constipation and pencil-like stools made its appearance. Three years before admission he started to drink and consumed up to a quart (1.1 liters) of whisky daily. For about a year cathartics were employed twice weekly because of the constipation. Four weeks before entering the hospital he began to vomit after meals, and later he vomited after the ingestion of any food. The vomiting was accompanied by severe epigastric pain, obstipation and loss of 25 pounds (11.3 Kg.) in weight. The physical findings at this time were not striking. There were moderate emaciation, epigastric tenderness and a palpable, tender colon. The gastric contents after an Ewald meal contained no free acid and only 14 degrees of total acid. Blood was constantly found in the stools. A blood count showed 4,220,000 red cells per cubic millimeter with 80 per cent (Sahli) hemoglobin. There were 8,000 white cells per cubic millimeter and an essentially normal differential count, with normal red cells in the smear. The Kahn reaction was negative. Roentgen examination of the gastrointestinal tract showed marked dilatation of the esophagus and a narrow constricting lesion involving the cardia and the pars media, with a niche deformity on the lesser curvature of the pars media, resembling an ulcer. The pylorus and the duodenum were normal. The roentgen diagnosis was syphilis or benign ulcer of the stomach. The clinical diagnoses were carcinoma of the stomach and spastic colitis, there being no serologic or clinical evidence of syphilis.

An exploratory laparotomy was performed (K.M.), and a small, contracted, scarred stomach associated with linitis plastica was found. The perigastric lymph glands were found to be enlarged. A total gastrectomy was done, together with the removal of 1 cm. of esophagus and 2 cm. of duodenum, and an esophagojejunostomy was performed. After a stormy postoperative course complicated by wound infection, parotitis and abscess formation, the patient recovered.

The resected stomach was much contracted, measuring but 12 cm. in length and 5 cm. in its greatest diameter (at the cardia). There were numerous irregular and stellate scars on the serosal surface, two of which produced constrictions. The mucosa was smooth. The microscopic sections showed a thickened mucosa, with increased production of mucus by the gastric glands, resulting in places in cystic dilatation; a thickened submucosa with a perivascular accumulation of round cells; increased interstitial tissue in the muscularis, with a perivascular accumulation of lymphocytes and plasma cells, and a thickened subserosa. The findings were interpreted as those of nonspecific chronic interstitial gastritis.



He was well for five years after the operation, during which time the red cell count remained over 5,000,000 per cubic millimeter of blood. He was partaking of an adequate diet, deficient only in fresh fruits, for which he claimed an intolerance. About one year before his second admission the red blood cell count began to drop; he began to lose weight and noticed occasional numbness of the fingers and toes. At this point he disappeared from our observation.

On his reappearance, a year later (six years after operation), he complained of weakness, pallor, increasing numbness of the hands and feet, loss of 20 pounds (9 Kg.) in weight and petechiae and ecchymoses of one month's duration. At this time he was pale; numerous ecchymoses were present on the body; the scleras were yellow, and the tongue was red at the tip and smooth along the margins. The knee and ankle jerks were hyperactive. The Babinski and Romberg signs were negative. Vibration sense was diminished at both ankles. There was no demonstrable lymphadenomegaly or hepatosplenomegaly. The blood picture was typical of pernicious anemia (see table). Both the direct and the indirect van den Bergh reactions were increased.

In spite of the fact that the patient claimed to have eaten an adequate diet, we wished to rule out the possibility of a deficiency in "extrinsic factor"<sup>5</sup> or of vitamin C. For this reason the patient was placed on a diet containing large quantities of these substances. During the three week control period he regressed both clinically and hematologically, though the petechiae and ecchymoses disappeared. At this time liver extract<sup>6</sup> was administered intramuscularly, and this was followed by a typical clinical and hematologic remission.

The bone marrow, which was studied both before and after liver therapy, showed the classic changes encountered in cases of untreated and treated pernicious anemia.<sup>7</sup> The first specimen showed extreme hyperplasia with marked preponderance of erythroid elements, a "left shift," a megaloblastic type of red cell maturation<sup>8</sup> and granulocyte maturation characterized by the presence of the bizarre megalometamyelocytes and band forms which typify the white cell maturation associated with pernicious anemia.<sup>9</sup> Marked activity was further substantiated by the presence of the many primitive cells and mitotic figures. The second specimen of marrow (obtained sixteen days after the beginning of liver therapy) was still hyperplastic, but the erythroid elements showed a decreased relative hyperplasia. Both erythroid and granulocytic maturation had reverted to normal, and the excessive numbers of both primitive cells and mitotic figures had disappeared. The observation on the bone marrow in no wise differed from those encountered in cases of classic primary pernicious anemia. The fact that even the changes in the marrow were so typical of pernicious anemia makes the diagnosis unquestionable, though of course it does not exclude the possibility of coincidence.

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# Blood Picture

Date	Red Blood Cells, per Cu. Mm.	Hemo- globin, %	Reti- culo- cytes	White Blood Cells, per Cu. Mm.	Poly- mor- phous, clear	Band Forms	Eosino- phils	Baso- phils	Lym- pho- cytes	Mono- cytes	Nucle- ated Red Blood Cells	Hemat- ocrit	Comment	Therapy
9/11/39	2,340,000	62	0.8	4,100	70	..	2	..	24	1	..	26	Anisocytosis ++++; macrocytosis + poikilocytosis +	High protein diet; ascorbic acid
9/19/39	1,880,000	60	0.8	4,930	72	12	..	..	25	3	..	..		
9/22/39	1,820,000	55	1.0	4,930	52	1	3	..	42	2	..	..		
9/29/39	1,520,000	53	1.8	7,350	77	6	..	..	17	6	..	..		
9/28/39	1,550,000	50	1.8	5,750	72	4	1	1	24	2	1	..		
10/ 2/39	1,610,000	55	1.2	8,450	87	10	1	1	10	1	..	..		
10/ 3/39	.....	..	...	.....	..	..	..	..	..	..	..	..	.....	Intramuscular liver extract
10/ 6/39	2,240,000	61	2.0	10,300	69	9	..	1	25	5	..	..		
10/ 7/39	.....	..	9.2	.....	..	..	..	..	..	..	..	..		
10/ 8/39	.....	..	23.0	.....	..	..	..	..	..	..	..	..		
10/ 9/39	.....	..	32.6	.....	..	..	..	..	..	..	..	..		
10/10/39	2,400,000	63	19.6	6,200	65	7	4	..	15	9	..	..		
10/11/39	.....	..	12.6	.....	..	..	..	..	..	..	..	..		
10/12/39	2,710,000	65	6.0	10,950	75	2	1	..	18	3	1	..		
10/17/39	3,330,000	71	2.8	9,250	71	10	2	..	19	8	..	38		

Hemoglobin: 15.6 Gm. = 100 per cent. (Evelyn photoelectric colorimeter.)

After the patient was discharged from the hospital he made one visit to the outpatient department and again disappeared from our observation. His final admission was four months later, when he entered the hospital in a critical condition, having taken a quantity of saponated solution of cresol five days previously. He died within forty-eight hours. On autopsy (performed by Dr. J. J. Kearns) there were gangrenous esophagitis and enterocolitis; edema and cloudy swelling of the viscera; acute glomerulonephritis, and an anatomically adequate esophagojejunal stoma with considerable dilatation of the jejunum. The only other observations of interest were the marked redness and hypertrophy of the bone marrow, which microscopically showed extreme hyperplasia. The red cell development had reverted to megaloblastic maturation.

#### COMMENT

Before discussing the pathogenesis of the pernicious anemia in our case it may be well to review briefly the present theories about the disease. It is fairly well substantiated that pernicious anemia develops when the "antipernicious-anemia factor" is absent.<sup>10</sup> This factor is produced in the gastrointestinal tract by the interaction of the so-called extrinsic, or food, and the intrinsic, or enzyme, factors, the latter being elaborated for the most part in the pylorus and the duodenum.<sup>11</sup> By this interaction an "anti-pernicious-anemia factor" is formed, which is absorbed from the intestine, stored in the liver and given off to the bone marrow (and undoubtedly at least to the nervous system) as function demands. Interference with this process at any point can and, as clinical reports have shown, does result in a pernicious anemia syndrome. That a tremendous factor of safety operates throughout is indicated by the relatively few patients with pernicious anemia encountered among large numbers of persons taking inadequate diets and having extensive gastric lesions, markedly increased gastrointestinal motility and severe damage to the liver.

As in all cases in which pernicious anemia develops after gastric operations, the possibility of coexistence must be considered. Certainly the fact that so few of the many persons who undergo extensive operations on the stomach have pernicious anemia would suggest this fact very strongly. We do not believe that this possibility can in any single instance be definitely ruled out. However, the statistical probability certainly makes coexistence extremely unlikely.<sup>12</sup>

One of the most interesting questions which arise is why pernicious anemia develops in some patients and not in others. One cannot search for the answer in animal experiments, since attempts with dogs,<sup>13</sup> pigs

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10. Castle, W.: *Am. J. M. Sc.* **178**:748 and 764, 1929. Castle, W.; Townsend, W. C., and Heath, C. W.: *ibid.* **180**:305, 1930.

11. Meulengracht, E.: *Am. J. M. Sc.* **197**:201, 1939.

12. Bloomfield, A. L., and Polland, W. S.: *J. Clin. Investigation* **14**:321, 1935.

13. Dragstedt, C. A.; Bradley, J. D., and Mead, F. B.: *Proc. Soc. Exper. Biol. & Med.* **33**:58, 1935.

and monkeys<sup>14</sup> have universally failed to reproduce the symptom complex recognized in man. These animals either show no changes or show changes demonstrable only when there is an added "strain," or at most a hypochromic, microcytic type of ("iron-deficient") anemia. It is significant that this type of anemia occurs in man with a frequency<sup>15</sup> estimated by various authors at from 20 per cent to 70 per cent.

Of further interest is the fact that not only extensive gastric resections but partial resections,<sup>16</sup> gastroduodenostomies and gastrojejunostomies<sup>17</sup> have resulted in pernicious anemia. The most simple explanation is found in cases such as ours and in others in which the stomach and part of the duodenum were destroyed, either by the underlying pathologic process or by an injurious agent.<sup>18</sup> Under such circumstances one has but to postulate a destruction or replacement of most of the portions of the intestine which elaborate the intrinsic factor to explain the findings. Since complete disappearance of the intrinsic factor need not be postulated, because a quantitative diminution suffices even in "primary" pernicious anemia,<sup>19</sup> it is more readily understood why occasionally partial or subtotal resections result in the same picture; the factor of increased motility, leading to briefer interaction of intrinsic and extrinsic substances at a suboptimal  $p_H$ , adds to the trend brought on by the quantitatively diminished intrinsic factor. When to this complicated picture is added the much curtailed and often inadequate diet so often taken by the patient, it is surprising indeed that pernicious anemia develops so rarely, and it must make one suspect that some added factor, perhaps a constitutional predisposition, is operating when major aberrations are encountered. With gastroduodenostomies and gastrojejunostomies probably the same factors operate, with the exception that there is, at least theoretically, little or no reduction in the quantity of intrinsic substance.

Aside from the purely theoretic considerations brought forth by a relatively rare finding, certain practical and significant facts become apparent. The most obvious of these is the fact that patients who undergo extensive surgical operations on the stomach must be observed indefinitely

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14. Bussabarger, R. A., and Ivy, A. C.: *Proc. Soc. Exper. Biol. & Med.* **34**: 151, 1936.

15. Hartfall, S. J.: *Guy's Hosp. Rep.* **84**:448, 1934. Lublin, H.: *Am. J. Digest. Dis. & Nutrition* **3**:8, 1936. Rieder, W.: *Zentralbl. f. Chir.* **61**:722, 1934

16. Fleischhacker and Klima.<sup>3a</sup> Rowlands and Simpson.<sup>3f</sup>

17. Alsted, G.: *Lancet* **1**:76, 1937. Lang.<sup>3d</sup> Larsen.<sup>3e</sup>

18. Goldhamer, S. M.: *Am. J. M. Sc.* **195**:17, 1938. Alsted.<sup>17</sup> Singer and Steigmann.<sup>2</sup> Sturgis and Goldhamer.<sup>3e</sup>

19. Goldhamer, S. M.: *Proc. Soc. Exper. Biol. & Med.* **32**:476, 1934. Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: *J. Clin. Investigation* **14**:708, 1935. Isaacs, R., and Goldhamer, S. M.: *Proc. Soc. Exper. Biol. & Med.* **31**:706, 1933

to anticipate (if possible) or at least to correct in its incipency the development of severe anemia and the accompanying neurologic degeneration. But much more important than the recognition of the relatively rare and usually obvious pernicious anemia is the correction of other, less obvious deficiency diseases brought about by an artificially perverted gastrointestinal function. Probably the most common of these is an iron-deficient state, resulting, in addition to the anemia, in suboptimal health. We feel that not only the diet but its utilization should be carefully evaluated periodically after operation, since, regardless of the success of the surgical procedure, the functional integrity of the upper part of the intestine is too often sufficiently changed to be inadequate under unexpected stress.

#### SUMMARY

A case of pernicious anemia developing five years after complete ablation of the stomach is reported and the pathogenesis considered. The importance of long-continued observation of patients who have undergone extensive gastric operations is stressed.

# SOME FACTORS IN A LOWERED MORTALITY RATE FOR ACUTE APPENDICITIS

ANALYSIS OF 2,013 CONSECUTIVE CASES

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Interest in the literature then appearing, which tended to show an increase in the death rate from acute appendicitis, led me in 1931 to survey the cases occurring in the Genesee Hospital, Rochester, N. Y., during 1930. The Genesee Hospital is of the semiopen type and therefore would lend itself to a cross section study of various methods of treatment and surgical technic used for this disease. There were 282 appendectomies in 1930. According to the methods then in use in surveying this subject, only cases in which the charts showed an unquestionably acute condition were accepted for this study. The criteria of acceptance were an accurate history of acute appendicitis, the physical findings as to temperature, pulse rate and condition of the abdomen and a description of the pathologic change found at operation, with a pathologic report on the removed appendix. Cases of chronic and subacute appendicitis or cases in which other operations were done, so as to cloud the issue, were not accepted. This principle has been followed in the subsequent analysis of cases used in this report. It was felt that only in this manner would an accurate picture of this important subject be obtained.

The data obtained are given in table 1. In keeping with the study of factors in the mortality rate then being used, sex and age incidence, delay in operation, anesthesia and time of operation were analyzed, and the results are incorporated in later tables.

In 1935 the problem was again taken up. It was thought that an analysis of all cases during a ten year period divided into two five year periods for comparison would elicit further, more accurate conclusions as to factors in the mortality rate. A study of all cases in which operation was performed in this hospital during the ten year period 1925 through 1934 allowed acceptance of 611 cases in the five year period 1925 through 1929 for comparison with 677 cases in the second five year period, 1930 through 1934. Table 2 shows the mortality rate in relation to the type of appendicitis and the total number of cases.

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Awarded the Paine Drug Company Award, May 1940, at the Rochester Academy of Medicine.

The mortality rate for each period showed only slight change. However, it was found that in the second five year period there was a rather decided decrease in deaths among patients with acute appendicitis complicated by local peritonitis, abscess or diffuse peritonitis. Following the principles laid down by such investigators as Walker,<sup>1</sup> Arnheim and Neuhof<sup>2</sup> and Black,<sup>3</sup> I analyzed, in addition to the factors mentioned in the 1930 survey, the preoperative and postoperative care of the patient and the type of incision used by the surgeon in performing appendectomy. With the factors of sex, age incidence and delay in reaching operation remaining the same in both periods and immediate operation undertaken without preoperative preparation, it was concluded

TABLE 1.—Data for 1930

Type of Appendicitis	Number of Cases	Deaths	Mortality, Percentage
Acute .....	85	0	0.0
Acute, with local peritonitis.....	21	0	0.0
Acute, with abscess .....	10	3	30.0
Acute, with diffuse peritonitis.....	17	5	29.8
Totals.....	133	8	6.01

TABLE 2.—Data for Two Five Year Periods

Type of Appendicitis	1925-1929			1930-1934		
	Number of Cases	Deaths	Percentage	Number of Cases	Deaths	Percentage
Acute appendicitis .....	501	2	0.398	480	7	1.45
Acute, with local peritonitis...	38	5	13.15	110	9	8.18
Acute, with abscess.....	39	9	23.0	43	7	17.2
Acute, with diffuse peritonitis.	33	11	33.3	44	10	22.2
Totals.....	611	27	4.41	677	32	4.72

that the improvement in the rate was due to better postoperative care of the patient. This care consisted of (1) attention to the fluid balance by greater use of parenterally or intravenously administered saline and dextrose solutions, (2) physiologic rest of the mind and the intestine by increased use of morphine and (3) discontinuance of giving fluids and food by mouth and futile enemas before the restoration of bowel tone. Treatment of nausea, vomiting and distention by the Wangenstein continuous duodenal suction was considered to be of life-saving value.

1. Walker, I. J.: A Comparative Mortality Study of Acute Appendicitis, *New England J. Med.* **208**:113-123, 1933.

2. Arnheim, E. E., and Neuhof, H.: Lowered Mortality in Acute Appendicitis, *Surg., Gynec. & Obst.* **59**:189-193, 1934.

3. Black, C.: Appendicitis Mortality in 1,605 Cases, *Illinois M. J.* **63**:231-239, 1933.

I felt, however, that one of the most interesting factors brought out in this study was the marked divergence as to mortality between patients operated on through a paramedian or a median incision and those for whom a McBurney incision was used. The results of this study are shown in table 3.

The right rectus, or paramedian, incision carried a mortality rate almost four times that of the McBurney incision in the less complicated cases and of over twelve times the latter rate in cases of the graver forms of the disease. I therefore concluded that the McBurney incision is the one of choice for appendectomy, especially in the complicated case. The opinion was advanced that extensive harmful operation through this incision in the hands of the occasional operator would be obviated.

TABLE 3.—*Data on Use of Different Incisions*

Complication	Paramedian Incision			McBurney Incision		
	Number of Cases	Deaths	Percentage	Number of Cases	Deaths	Percentage
Local peritonitis						
1925-1929.....	18	4	22.2	20	1	5.0
1930-1934.....	59	3	5.0	49	1	2.0
With abscess						
1925-1929.....	25	6	24.0	14	2	14.3
1930-1934.....	18	4	22.2	26	1	3.8
Diffuse peritonitis						
1925-1929.....	23	11	48.0	10	0	0.0
1930-1934.....	22	15	60.0	22	1	4.5
1930: 3 paramedian to 1 McBurney; mortality rate, 6.75%						
1934: 1 paramedian to 4 McBurney; mortality rate, 2.00%						

From this study one other interesting and outstanding factor was produced. My interest in the use of drainage in cases of the acute phlegmonous type of appendicitis began in 1927, when a small series of cases was reported by me in which closure without drainage had been employed. At that time drainage was invariably used for this type of condition. My attention was unfortunately not directed so much to its effect on the treatment of appendicitis as to the earlier discharge of the patient from the hospital and his earlier return to gainful employment. I felt that closure without drainage in conjunction with the use of the McBurney incision accomplished this purpose. I felt also that the wounds of all patients with appendicitis without gangrenous changes could be closed. In further developing this study it was found that secondary abscess formation had occurred in 17 of 343 patients for whom drainage had been employed and in only 2 of 352 patients whose wounds were closed without drainage. A tentative conclusion was put forth in the summary of the paper presented in 1935 that drainage of the appendectomy wound does not prevent formation of peritoneal abscesses.



With the belief that the mortality rate should show a decided improvement resulting from use of the principles laid down in 1935 and also that the subject should be occasionally brought before the staff so as to maintain an appendicitis-conscious attitude on the part of the physician and the surgeon, this ten year study has been further augmented by the analysis of 1,255 cases of appendicitis in which operation was performed in the Genesee Hospital in the four year period 1935 through 1938. Three hundred and six cases were accepted for an incidental study of interval acute exacerbation of a chronically inflamed appendix and of the patient with early acute appendicitis. In this series 725 cases of proved acute appendicitis were used.

A change in nomenclature used by the record office was made in 1935. This change is now being accepted throughout the United States and offers a better classification of the disease and one which will allow a uniformity which hitherto has been impossible to obtain in reports on

TABLE 4.—*Mortality for Different Types of Appendicitis (1935-1938)*

Type of Appendicitis	Number of Cases	Deaths	Mortality, Percentage
Acute .....	518	0	0.0
Acute gangrenous .....	91	3	3.3
Acute, with perforation.....	63	5	7.5
Acute, with abscess.....	48	8	17.02
Totals.....	725	16	2.2

this condition. The present literature is very confusing as to the type of appendicitis discussed. Table 4 contains the data obtained as to the new classification and the mortality rate for each class and for the 725 cases.

Most writers on this subject adjust the death rate, eliminating those deaths which are not operative or which are proved due to other causes than extension of the infection within the abdominal cavity. In this series, 1 patient died from diabetes, autopsy proving the appendicitis to be controlled. Two patients died of pulmonary embolism. Two were moribund on admission, their condition permitting no treatment during their one and one-half hours in the hospital. Another patient was admitted to the hospital in coma. No operation was feasible. Autopsy showed a ruptured appendix. One, who had been operated on twice previously at another hospital, was admitted in an extremely precarious condition, and no further operation was deemed advisable. The last patient was admitted with peritonitis apparently due to infection following abortion. Autopsy showed a ruptured appendix. The status in this case was never sufficiently cleared to place the pathologic process which truly caused death. A corrected rate is shown in table 5, from

which it will be seen that the incidence of operation for acute appendicitis has increased in the Genesee Hospital 25 per cent over that for the previous five year period, with a decrease in the mortality rate of 50 per cent. The factors in this decrease are discussed here. The study of these factors is based on an analysis of 2,013 consecutive proved cases of acute appendicitis observed in this hospital in the years 1925 through 1938.

## ETIOLOGY

No actual data were obtained as to the number of patients admitting one or more previous attacks. I believe the percentage to be fairly high. In the study of the patient with chronic appendicitis a fair degree

TABLE 5—*Increase in Incidence and Decrease in Mortality*

Year	Number of Cases	Deaths	Mortality, Percentage
1930	133	8	6.01
1931	131	7	5.34
1932	138	6	4.4
1933	128	4	3.12
1934	147	2	1.36
Total	677	27	3.98
1935	144	5	3.4
1936	186	2	1.2
1937	196	5	2.7
1938	199	1	.5
Total	725	13	1.95

TABLE 6—*Sex Incidence*

Type of Appendicitis	Ratio
Recurrent or interval .....	7 females to 1 male
Acute exacerbation of chronic.	2 females to 1 male
Early acute .....	1 female to 1 male

of information as to the pathologic picture and the symptoms was obtained. One hundred and seventy-three were operated on for recurrent or interval attacks, 115 for acute exacerbation of chronic appendicitis and 18 for early acute appendicitis. The patients last mentioned might well have been added to the group with acute appendicitis, as the difference lay only in the macroscopic description given by the surgeon.

The sex incidence in this group is interesting. In cases of interval or acute exacerbation of chronic appendicitis, the female patients apparently complained of pain in the lower right abdominal quadrant much oftener than did the male patients. Only as the condition found at operation approached early acute inflammation did the ratio of 1 female to 1 male, as found in the analysis of acute appendicitis, hold true. Table 6 shows the sex incidence.



# RESULTS OF APPENDECTOMY FOR PAIN IN THE RIGHT LOWER QUADRANT

All surgeons have had the disappointing experience of failure to cure pain in the lower part of the abdomen by appendectomy. This failure has led to adoption of a policy in the Genesee Hospital of making a thorough study of the patient seeking relief from this complaint to rule out, if possible, any existing pathologic process other than appendicitis. If none is found, it is explained to the patient that no prognosis is given as to cure, but that, no other cause having been found to account for his trouble, appendectomy is elective. This is stated on his chart before operation. I have been able to follow 72 of these patients. The results of this follow-up are tabulated (table 9).

TABLE 9.—*Results of Follow-Up*

Cases Followed	Percentage of Total	Cures	No Result	Per Cent of Failure
72 .....	20	59	13	20

TABLE 10.—*Duration of Symptoms Before Operation (1930)*

Type of Appendicitis	Duration of Symptoms	Average Duration of Symptoms, Hours
Acute .....	5 hours to 3 days	24
Acute gangrenous .....	5 hours to 8 days	48
Fatal cases .....	10 hours to 14 days	84
All fatal cases, 1930-1934.....	10 hours to 14 days	84.5

Of the 59 patients rated as cured, 8 had thorough study, which included cystoscopic examination. Of the 13 without result, only 1 had had complete study. In 7 patients no further pathologic change could be found to account for the failure. Study of the others showed the causative pathologic process to be: (1) chronic ulcerative cystitis; (2) cholelithiasis (2 cases); (3) stricture of the ureter (1 case); (4) ureteral calculus (1 case), and (5) stone in the common duct (1 case).

Thus it is to be seen that with complete study before removal of the appendix for pain in the right lower abdominal quadrant good results may be obtained. Careless surgical intervention may result only in the one saving grace that the patient will not suffer the possibility of future rupture of the appendix.

## FACTOR OF DELAY AND ITS EFFECT UPON THE MORTALITY RATE

The charts for the year 1930 allowed, in a fair percentage of the cases, compilation of data on the average delay before surgical treatment was instituted. The results for that year are given in table 10.

The charts for the last period revealed a much more complete and accurate description of the entire case, which allowed in 615 cases

accurate study of the duration of symptoms before admission of the patient to the hospital; the results are shown in table 11. It is evident from this table that the patient with appendicitis is not reaching the operating table at an earlier hour than in the previous two periods. The effect of this factor was studied as to both the average duration of symptoms (table 12) and the ratio of the number of patients with the advanced condition admitted in each year to the number of deaths occurring in that year (table 11).

It is certainly quite evident from table 12 that if all patients with acute appendicitis were operated on within twelve hours from the onset of the disease the mortality would be lowered to an irreducible minimum. And it is also evident that operation within twenty-four hours

TABLE 11.—*Duration of Symptoms Before Operation (1935-1938)*

Type of Appendicitis	Average Duration of Symptoms, Hours
Acute inflammatory .....	27.8
Acute, with gangrene .....	42.3
Acute, with perforation .....	45.3
Acute, with abscess.....	98.8
Fatal .....	80.0

TABLE 12.—*Effect of Delay in Operation*

Average Duration of Symptoms	Number of Cases	Percentage of Total	Deaths	Mortality, Percentage
12 hours	192	31.2	0	0
24 hours	195	31.7	1	0.5
. Total within 24 hours.....	387	62.9	1	0.25

would result in only an occasional death. One hundred and ninety-two patients, or 31.2 per cent of all observed in the past four years, fell in the first favorable grouping, with no deaths. One hundred and ninety-five, or 31.7 per cent, were admitted within twenty-four hours, with only 1 fatality, giving a total of 387 operated on within the optimum time and incurring a mortality rate of only one fourth of 1 per cent. The picture is sadly different when the disease has progressed for from forty-eight to seventy-two hours, which occurred in 28 per cent of all cases, with a sharp rise to a mortality rate of almost 10 per cent in this group.

A tabulation of the ratio of cases of advanced appendicitis to the total number of cases in each year shows that, as this total reaches 35 per cent, 1 in 6 or 8 patients dies, whereas a reduction in this number to under 25 per cent will produce a 33.3 per cent reduction in the death rate, so that only 1 in 22 to 25 will die of the disease.

What more eloquent appeal is necessary than table 14, which shows that the first step in reduction of mortality from appendicitis is early

operation? This can be accomplished in only two ways; the first is continued education of the public in early consultation with the physician for acute abdominal conditions, and the second is continued education of the physician in the early diagnosis of appendicitis and immediate operation. Some attempt has been made along these lines in Rochester, N. Y., and perhaps explains in part the good rate, but continued reeducation has not been followed as far as the public is concerned; certainly the physician should have been made appendicitis conscious by the innumerable articles and talks on this subject. That acute appendicitis per se does not kill should be a well recognized fact, as should the fact that it is the onset of spreading infection, with its attendant shock.

TABLE 13.—*Effect of Further Delay*

Average Duration of Symptoms	Number of Cases	Percentage of Total	Deaths	Mortality, Percentage
48 hours	120	19.5	4	3.3
72 hours	52	8.4	5	9.6
4 to 9 days	53	8.4	0	0.0
10 to 20 days *	3	18	3	100.0

\* Delayed by failure of diagnosis.

TABLE 14.—*Mortality in Relation to Advanced Involvement*

Year	Number of Cases	Percentage of Total	Deaths
1930	48	36	1 in 6
1931	43	33	1 in 8
1932	37	27	1 in 6
1933	33	26	1 in 8
1934	35	23	1 in 12
1935	60	41.7	1 in 8.5
1936	45	25	1 in 22
1937	57	31	1 in 10
1938	44	25	1 in 25

obstruction from ileus, with terminal nephritis and pneumonia, that kills. In my series this was the causative lethal agent in 83 per cent of the cases. Any factor tending to prevent this dangerous complication is of value. Until constant reeducation produces a minimum of cases of advanced involvement the battle will be fought in the hospital and in the surgery, and recognition of certain factors of help in that battle is essential. Some of the factors are discussed here.

#### RELATION OF SEX TO MORTALITY

The greater susceptibility of the male to the ravages of appendicitis has been mentioned. This was evident in our series for 1930 to 1934, and further data, obtained for the nine year period, are shown in table 15.

A yearly variation is evident as to mortality in the two sexes, higher in one year and lower in the next, but for the total number of cases

in the two periods the female shows a lower mortality rate. We feel that the variation is not due so much to a greater susceptibility of the male as to the female anatomic character, which allows of greater ease of detection of secondary abscess formation and subsequent extraperitoneal drainage. The chance to drain the male rectally is too infrequently met with; it occurred in our series in only 3 cases, as compared with 12 in which posterior colpotomy could be done in the female. The male is thus more often subjected to secondary intraperitoneal operative manipulation with all its hazards.

#### RELATION OF ANESTHESIA TO MORTALITY

In the survey of 1930 anesthesia was considered, and the conclusion was reached that nitrogen monoxide without ether was the anesthetic

TABLE 15—*Sex Incidence in Relation to Mortality*

Year	Males			Females		
	Number of Cases	Deaths	Mortality, Percentage	Number of Cases	Deaths	Mortality, Percentage
1930	71	5	7.03	62	3	3.19
1931	76	4	5.00	53	4	7.5
1932	68	4	5.88	66	3	4.5
1933	85	3	3.52	49	2	4.0
1934	73	4	5.4	74	0	0.0
Totals.	373	20	5.3	304	12	3.9
1935	81	4	3.7	63	3	6.3
1936	84	0	0.0	103	2	1.9
1937	96	4	4.1	100	2	2.0
1938	96	1	1.0	102	0	0.0
Totals	357	9	2.5	365	7	1.9
Cases of Advanced Involvement						
1935-1938	108	9	(1 in 12)	120	7	(1 in 17)

of choice, as it carried a morbidity rate of 4.4 per cent as compared to 17 per cent in cases in which ether, alone or combined with nitrogen monoxide was used. The anesthesia department of this hospital consists of trained medical specialists in this field who are constantly keeping in touch with the latest developments, and since 1936 cyclopropane has been the predominant anesthetic agent. This has not only done away with the necessity for the use of ether in many cases but has overcome the objection, frequently cited, of lack of relaxation of the patient for the surgical procedure. The fact that cyclopropane allows a high oxygen concentration, which nitrogen monoxide and ether does not allow, may be of the utmost importance in its success (Wright). Spinal anesthesia has been said by some writers, lately Collins,<sup>4</sup> of Los Angeles, to have been a factor in the reduced mortality. It has been reserved in this series for those patients in whose cases use of an inhalation anesthetic seemed contraindicated and has also been used for some very ill patients,





were 10 children under 10 years of age, or 20.8 per cent of all patients with walled-off abscesses, and 23 patients over 40 years of age, representing about 48 per cent of the total number with abscess formation. Therefore I feel that they do have the power of localization, and analysis of these groups points out that the causative factor is decidedly failure of early diagnosis. Table 18 shows that whereas only 17.8 per cent of the patients between the ages of 11 and 40 years are admitted with ruptured appendixes, thus falling into the low mortality group as given in table 12, those under 10 years of age showed 35.9 per cent and those over 40 years 53.6 per cent of ruptured appendixes, which throws them

TABLE 17.—*Age Incidence in Relation to Mortality*

Age	1930-1934			
	Number of Cases	Deaths	Percentage of Cases	Percentage of Mortality
1-10	89	9	11.6	29.0
11-40	435	6	70.0	19.4
41-80	140	17	18.8	51.6
1935-1938				
1-10	89	3	12.6	18.7
11-40	494	1	70.0	6.3
41-90	123	12	17.4	75.0

TABLE 18.—*Age Incidence of Ruptured Appendix*

Age, Years	Number of Cases	Ruptured	Percentage of Advanced Type
1-10	89	32	42.6
11-40	494	88	18.0
41-80	123	66	54.5

into the high mortality group. The greatest difficulty in the diagnosis of appendicitis is apparently encountered in these two age groups.

That the same factors apply to children, i. e., susceptibility to the disease, duration of symptoms, good results with early operation and the acquired resistance within themselves to combat the disease as in the average case of appendicitis, may be proved by table 19; the data are obtained from all children under 15 years of age in this series.

Even in these groups, which carry a high percentage of the mortality rate, no patient operated on within twenty-four hours died, and again it must be repeated that to lower the mortality rate physicians and surgeons who suspect involvement of the appendix should not delay their diagnosis for more than two to four hours at a maximum. If appendicitis then is still to be considered, an attitude may rightfully be adopted that to operate on suspicion is far more creditable than to delay, since it will obviate rupture of the appendix.

## CATHARSIS: RELATION TO MORTALITY

As has been mentioned, the histories in this series may be labeled complete, so that the factor is fairly accurate. The deleterious effect of catharsis on patients with appendicitis has been mentioned in almost all articles since 1930. (The data as to years, deaths and type of cases are contained in table 18.) Lately the use of enemas before operation has been stressed as also injurious. I feel that in my series this factor was of minor significance. In the past four years only 40 patients had a history of catharsis, and in only 1 death was there cause to consider it as a factor. The patient was a boy admitted to the hospital in a moribund

TABLE 19.—*Preoperative Duration of Symptoms in Children Under 15 Years of Age*

Operated On Within	Number of Cases	Death	Mortality, Percentage
12 hours	37	0	0
18 hours	7	0	0
24 hours	38	0	0
Total within 24 hours.....	82	0	0
48 hours	25	1	4.0
72 hours	10	1	10.0
4th, 5th, 6th, 7th day	15	1*	6.6

\* Moribund on admission; no operation.

TABLE 20.—*History of Catharsis*

Year	Abscess	Deaths	Perfora- tion	Deaths	Gangrene	Death	Acute	Deaths
1935.....	3	1	4	1	1	0	0	0
1936.....	1	1	3	0	0	0	7	0
1937.....	1	0	3	0	1	0	0	0
1938.....	2	0	2	0	2	0	9	0
Total.....	7	2	12	1	5	0	16	0

condition, with a history of symptoms for six days. Many cathartics and enemas had been given. Although catharsis is harmful and education of the public is essential to prevent its use in cases of acute appendicitis, other factors are of far greater importance.

## INCISIONS USED AND MORTALITY RATES WITH EACH

In table 3 the wide divergence in the mortality rate in the McBurney and the right rectus, paramedian, was shown. Further study of this factor, which I believe to be one of the most important findings of my 1935 survey, shows the mortality rates for the incisions in the three periods for comparison. Owing to the change in nomenclature this study is based in this table on the advanced type of condition in each period.

The mortality with the paramedian incision was three and one-half times greater in the first period and five times greater in the second and, even with many other factors shown to be improved in the treatment of the patient with appendicitis, was still one and a half times greater than that noted with the McBurney incision in the last period. I therefore feel that my conclusion in 1935 that the McBurney incision is the one of choice for appendectomy, especially for advanced appendicitis, is still logical.

Another factor concerns the follow-up of the patients operated on with these two incisions. This was possible in 205 of the cases. One hundred and seventy-two patients with McBurney incisions returned. Nineteen had had infected wounds; there were 28 in whom drainage had been

TABLE 21.—*Further Study of Incisions*

Years	Number of Cases	McBurney Incision: Mortality, Percentage	Number of Cases	Paramedian or Median Incision: Mortality, Percentage
1925-1929.....	...	9.3	...	31.1
1930-1934.....	...	4.7	...	23.3
1935-1938.....	...	5.5	...	8.9
All Cases				
1935-1938.....	539	1.48	142	3.5

TABLE 22.—*Results with Different Incisions*

Type of Incision	Number of Cases	Anatomically Good Result	Weakness	Hernia	Disability
McBurney.....	172	171	0	1	0
Right rectus.....	33	28	1	4	4

employed. There was 1 hernia in a case in which drainage had been done. No sac was found at operation to correct the hernia; a defect in the internal oblique muscle was discovered and easily repaired. This operation was done originally by a senior house surgeon. Of the 33 patients with right rectus incisions who returned, only 3 had been drained. Each of the 3 had a hernia. Of the 33 patients, 28 were given a perfect rating; 1 had a weakness of the incision, and there were 4 herniations, with economic disability.

Thus, with 1 in 7 patients for whom the paramedian incision was used showing postoperative herniation and 1 in 8 with economic disability, surgeons must give careful thought to the choice of the incision, especially if drainage through this incision is a possibility. I feel that the McBurney incision is entirely adequate for surgical treatment of the appendix, limits the field of operation to this region, allows earlier

discharge of the patient from the hospital and, even with drainage and infection of the incision, is a safeguard against postoperative herniation and economic loss.

#### DRAINAGE AS RELATED TO MORTALITY RATE

As invariable in past years as use of the right rectus incision in all cases of suspected acute appendicitis was the use of drainage for patients showing at operation a process that had progressed further than an early acute state. The drains used were of the handkerchief, coffer dam and hard rubber tube types. Their purpose was to drain the abdominal cavity of the infection produced by the appendicitis and to prevent the formation of secondary abscesses. No thought was given to the possibility that the exudate might be a protective reaction possessing some curative powers. Results of experiments in the late twenties<sup>3</sup> and of studies on the absorptive and protective powers of peritoneum led

TABLE 23.—*Drainage in Relation to Mortality Rate*

	1925-1929		1930-1934		1935-1938			
	Drained	Closed	Drained	Closed	Advanced Cases		Total Cases	
					Drained	Closed	Drained	Closed
Number of cases.....	98	12	245	340	134	79	134	518
Complications								
Abscess.....	11	0	6	2	19	6	19	8
Fecal fistula.....	4	0	2	0	2	0	2	0
Obstruction.....	4	0	1	0	0	0	0	0
Evisceration.....	1	0	0	0	0	0	0	0
Perforation of cecum..	2	0	3	0	0	0	0	0
Hernia.....	8	0	1	0	3	0	4	0
Infected wounds.....	2	0	12	28	9	18	9	38

to closure of some wounds in the advanced type of condition (Shipley;<sup>6</sup> Rhodes and his co-workers;<sup>7</sup> Buchbinder;<sup>8</sup> Collins<sup>4</sup>). I pointed out in 1935 that secondary abscess occurs more frequently in drained wounds than in those closed without drainage. Further study of this factor is presented in table 23.

My statistics show that in the five year period 1925 to 1929, in cases of advanced disease only, 98 patients were drained with subsequent occurrence of secondary peritoneal abscesses in 11, infected wounds in 2.

5. David, V. C.: Peritonitis: An Experimental Study, *Surg., Gynec. & Obst.* 45:287-293, 1927. David, V. C., and Sparks, J. L.: The Peritoneum as Related to Peritonitis, *Ann. Surg.* 88:672-677, 1928.

6. Shipley, A.: Appendicitis with Peritonitis: Treatment Without Drainage, *South. Surgeon* 3:308-315, 1934.

7. Rhodes, G. K.; Birnbaum, W., and Brown, M. J.: Acute Appendicitis: Clinical Review of One Thousand Consecutive Cases, *California & West. Med.* 45:458-463, 1936.

8. Buchbinder, J. R.: Surgical Treatment of Acute Peritonitis, *Surg., Gynec. & Obst.* 59:485-490, 1934.

fecal fistulas in 4 and postoperative obstruction in 4, with recovery in only 1 instance of the last-mentioned complication. Eight patients had ventral hernias. The wounds of only 12 patients were closed without drainage, and no complications occurred in this group. Perforation of the cecum at the point of drainage was observed at autopsy in 2 cases in the group treated with drainage.

In the second five year period, of the total number of cases drainage was employed in 245. Secondary peritoneal abscess occurred in 6 patients; 4 had fecal fistulas, and 3 of these recovered. One patient died from intestinal obstruction. A perforated cecum was observed at autopsy in 3 cases. Infected wounds were treated in 12. A subsequent readmission in 1 case was for repair of a ventral hernia in the appendectomy incision.

Closure without drainage was done in 340 cases in this period, with only 2 secondary abscesses; 28 patients had infected wounds, without other complications.

In the last period in the "advanced" classification only 134 patients were treated with drainage, with 19 secondary abscesses, 9 infected wounds, 2 fecal fistulas and 3 postoperative hernias. No drainage was used for 79 of these patients; there occurred abscess in 6 cases and 18 infected incisions in the total number of patients; the wounds of 548 were closed during this period, with 8 abscesses and 38 infected wounds.

The notation on infections, which seem to show that these occur more frequently in undrained wounds, are, I believe, very misleading. The incidence as given shows infection to occur in 1 in 14 cases, or 6.9 per cent of the wounds closed without drainage and 1 in 17, or 5.9 per cent, of the drained wounds. This report is based on those cases in which a notation was made of removal of sutures and simple spreading of the incision or in which incision and drainage with the patient under anesthesia had been done. The final discharge note in those cases in which drainage was instituted almost constantly showed the patients to be leaving the hospital with a draining sinus. Another type of wound infection, encountered in this series in 3 instances as part of the picture of fatal complications, was gas bacillus infection of the abdominal wall in cases in which drainage had been used. The inclusion of these and of 8 cases in which there were fecal fistulas would raise the incidence of infected wounds in cases of drainage above that for wounds closed without drainage.

Cases of obstruction mentioned in this series are those proved by autopsy, except in 1 instance, in which obstruction was proved at operation, with cure. The relation of this complication to the mortality rate is shown in table 24.

Analysis of these deaths shows that in the 4 cases of the first period handkerchief drains had been used in 1 and rubber tube drains in 3.

In the case in the second period the wound was drained by two split rubber tubes.

The same holds true for deaths from perforated cecums, of which there were two in the period from 1925 to 1929 and three in that from 1930 to 1934, with none from 1935 to 1938. In all of these cases rubber tube drains had been used.

In the ten year period from 1925 to 1934 the occurrence of five fatal pulmonary emboli, all in cases of drainage, was noted. This complication has not happened in the series for 1934 to 1938.

A comparison of the mortality rates with and without drainage is given in table 25. These data are based on the study of cases falling

TABLE 24.—*Obstruction in Cases of Appendicitis*

Years	Deaths from Obstruction	Percentage of Deaths
1925-1929	4	16 0
1930-1934	1	3 2
1935-1938	0	0 0

TABLE 25.—*Mortality Rate With and Without Drainage*

Years	Number Drained	Mortality, Percentage	Number Not Drained	Mortality, Percentage
1925-1929	98	24.5	12	0 0
1930-1934	175	14.5	22	0 0
1935-1938	134	9.7	79	1.26
<b>Total cases *</b>				
1930-1934	245	11.48	340	0.88
1935-1938	156	7.7	548	0.18

\* As inclusion of the cases with abscess formation might raise a question, as in such cases drainage should be and invariably is carried out, the following data are incorporated in this table with this type of case omitted.

1930-1934	132	13.6	22	0 0
1935-1938	91	5.95	78	1 25

in the classification of advanced appendicitis. This is the group in which drainage was almost universally used until 1930.

In the series from 1930 to 1934, drainage was used in 24.7 per cent of all cases, with a mortality rate for that period of 4.72 per cent. In the period from 1935 to 1938, only 21.5 per cent of all wounds were drained, and the mortality rate for this period was 1.95 per cent.

It is therefore evident from these statistics that drains do not drain the peritoneal cavity. Secondary peritoneal abscesses occur more frequently with drainage than without it. I believe that wound infection is as frequently or even more frequently met with when drainage is used, that it is conducive to postoperative herniation and that it seems to be a factor in the occurrence of fatal perforation of the cecum and fecal fistula. Study of the autopsy observations in these cases shows

that the drain is encapsulated with necrotic material, that abscesses are scattered throughout the drained area and that this pathologic change has occurred despite the theory that drainage would prevent it. The employment of drainage has not prevented the fatal outcome of the case, nor, in this series of cases, has closure of the wound without drainage in cases of advanced appendicitis raised the mortality rate as it was first thought that it might. The data in table 25 show that with almost seven times the number of patients not drained in the years 1935 to 1938 and four times the number of wounds closed without drainage in the period from 1930 to 1934 over that from 1925 to 1929, the mortality rate was not only reduced one half, but the mortality was almost entirely confined to the patients for whom drainage was employed. This may be attributed partly to the lack of deaths in the past eight years in this series from obstruction and ileus (table 23). The last enterostomy done for postoperative ileus in the Genesee Hospital was performed in 1930. In the years 1925 to 1929, 3 patients had ileostomies, 2 for ileus and 1 for obstruction due to adhesive bands, found on exploration. One exploration for ileus was done in 1931, but none was found. All cases ended fatally. Wounds were drained in early periods by handkerchief drains, and later by rubber tubing. It is to the disappearance of these drains from use that I attribute the disappearance in these cases of postoperative obstruction, intractable ileus and perforation of the cecum. Fetal fistula, which used to be considered a common finding, has also been a rare complaint in the last series at this hospital.

#### TREATMENT OF THE STUMP

In 83.6 per cent of all cases in which operation was performed in the years 1935 to 1938 the appendical stump has been either ligated and dropped back or incorporated by its tie in the mesentery. In 119, or 16.4 per cent, an inversion technic has been used.

A study of all deaths due to appendicitis occurring in the hospital since 1921 reveals no evidence that either of these technics has contributed to the mortality. One patient from whom an "interval appendix" was removed with difficulty due to a retrocecal position and many firm fibrous adhesions was treated by simple ligation and dropping back of the stump. A secondary abscess subsequently developed in the right flank. It is believed that the stump became fixed in a low point in the lateral gutter, in a small collection of blood from minute oozing of the separated adhesions. An objection to the inversion technic is presented by the subserous hematomas which occasionally form in the suture line. I am now inclined to follow the technic advocated by Ochsner<sup>9</sup> in selected cases in which inversion seems indicated and to do so without tying the stump.

9. Ochsner, A.: *The Technique of Appendectomy*, *Surgery* 2:532-552, 1937.

## REMOVAL OR SIMPLE DRAINAGE FOR ACUTE APPENDICITIS

In all cases of disease classified as acute appendicitis, acute gangrenous appendicitis and acute appendicitis with perforation the appendix was removed. In many instances this required considerable manipulation. Appendectomy was done in 35 cases with abscess formation. In 12 cases in which abscess was present no attempt at removal was undertaken. Therefore it may be said that, except in some cases of appendical abscess, the mortality rate has been obtained on a basis of appendectomy. The rates are given in table 26.

The picture obtained from table 26 would seem to show that simple drainage carries a mortality five times that of appendectomy in all cases of advanced appendicitis and twice that of appendicitis with abscess

TABLE 26—*Results of Simple Appendectomy and of Simple Drainage*

Type of Appendicitis	Number of Cases	Appen- dectomy	Drainage	Deaths	Mortality, Percentage
Acute, with gangrene .	91	91	.	3	3.3
Acute, with perforation	66	66	.	3	4.5
Acute, with abscess .	47	35	.	4	11.4
Acute, with abscess .	..	..	12	3	25.0
	204	192	.	10	5.2
			12	3	25.0

TABLE 27.—*Effect of Manipulation on Mortality*

	Number of Cases	Deaths	Mortality, Percentage
Appendectomy—no manipulation ..	15	0	0.0
Manipulation to remove ...	21	4	19.0
Simple drainage—no manipulation	9	0	0.0
Attempt to remove .. .. .	3	3	100.0

formation. This holds true only with a certain technic. Further investigation of this subject will show that in cases in which simple appendectomy without disturbance of the protective barriers was done no deaths occurred, and in those in which simple drainage was done without an attempt to find the appendix this also held true. However, in cases in which an abscess was found and ruptured to explore and remove the appendix and in those in which an unsuccessful exploration was done in an attempt to remove the appendix, deaths followed (table 27).

It is thus evident that appendectomy done in such a manner that a large abscess is ruptured and the contents are allowed to spill into the general peritoneal cavity superimposes a toxic reaction, which becomes lethal in some cases. It is my belief that timing of the surgical procedures enters into this problem. Study of the deaths occurring under these circumstances showed in some cases that the temperature and



pulse had tended toward normal when the surgical procedure was undertaken, with an immediate sharp rise and ensuing death. In these cases the condition had not been allowed time to “cool” or to utilize or form all of the protective barriers in walling off the infection. The operation, besides being premature, was of such a nature that instead of an approach directly over the localization existing barriers were broken down, resulting in “surgically spread peritonitis.” These observations correspond to the data obtained by Bower<sup>10</sup> and published in January 1939. He described his protective zones and advocated delayed operation and serum treatment with an unroofing approach to the localized abscess. Serums may play some part in this regimen. I have had no experience with their use and rather feel from my investigations that proper localization and a proper approach by means of the McBurney incision or some other suitable muscle-splitting incision in the flank will reward surgeons by a greatly reduced mortality rate.

DELAY OR IMMEDIATE OPERATION

Delay versus immediate operation for acute appendicitis has been a topic of discussion in most of the publications dealing with appendicitis

TABLE 28.—*Mortality Rate According to Day of Disease on Which Operation Was Done*

Days.....	1st	2d	3d	4th	5th	6th	7th	8th	9th	11th	16th	20th
Number of Cases..	192	195	120	52	27	6	10	7	3	1	1	1
Deaths.....	1	2	5	2	0	0	0	0	0	1	1	1
Mortality, Percentage.....	0.5	1.0	4.1	3.8	0	0	0	0	0	.....100.0.....		

since Stanton<sup>11</sup> pointed out that the mortality rate increased with every twenty-four hours of symptoms until after the sixth day, when it tends to the level observed for patients operated on within twenty-four hours. This has been shown in table 12, but it is more accurate when based on operation on the day of the disease as given in table 28.

The data shown follow the observation of Stanton and warrant consideration as a factor in the death rate from appendicitis. Immediate operation has been the policy of all surgeons in the Genesee Hospital throughout the first and the second five year period. In the past four years 7 patients have been treated by delayed operation. For only 1 was the true Ochsner regimen used. The results are tabulated in table 29.

10. Bower, J. O.: The Lucid Interval and Acute Appendicitis, *Am. J. M. Sc.* **195**:529-538, 1938; Spreading Peritonitis Complicating Acute Perforative Appendicitis, *J. A. M. A.* **112**:11-16 (Jan. 7) 1939.

11. Stanton, E. M.: Acute Appendicitis, *Surg., Gynec. & Obst.* **59**:738-744, 1934.

Analysis of the deaths in the past eight years brings out some factors which would seem to indicate that further thought should have been given to the use of a delayed form of treatment in some of these cases.

In the period from 1930 to 1934, 17 of the 33 patients who subsequently died were subjected to immediate operation in the presence of severe toxemia as shown by high fever and pulse rate. Four of these had temperatures of 104 F. and 1 had a temperature of 105 F. with a pulse

TABLE 29.—*Delayed Treatment of Appendicitis*

Case 1:	Boy aged 11; moribund on admission; no operation advised; ill 6 days at home, with history of many doses of castor oil and enemas; temperature 101 F.; pulse rate 100; leukocyte count 32,600 per cubic millimeter, with 76% neutrophils; Ochsner treatment instituted; died in 12 hours; autopsy; tip of appendix sloughed off; toxic ileus; no obstruction
Case 2:	Girl aged 11; duration of symptoms 6 days; sulfanilamide medication; temperature normal on 8th day; pelvic abscess drained by posterior colpotomy; sent home; operated on six months later; appendix removed; follow-up 5 months later; rated as cured
Case 3:	Woman aged 22; duration of symptoms 48 hours; temperature 102 F.; pulse rate 148 on admission; leukocyte count 27,000 per cubic millimeter, with 88% neutrophils; preoperatively, 13,800, with 79% neutrophils; operated on 8th hospital day; midline incision; appendix had sloughed out; fecalith found free; drainage through stab wound in right side; discharged 25th day in hospital; improved
Case 4:	Woman aged 40; duration of symptoms 7 days; temperature 101.3 F.; pulse rate 130; leukocyte count 20,500 per cubic millimeter, with 80% neutrophils; operated on 8th day in hospital; incision of abscess through anterior wall of rectum; cultures showed streptococcus, B. coli and staphylococcus; discharged 22d day in hospital
Case 5:	Man aged 38; ill at home for 3 weeks; temperature 101 F.; pulse rate 86; leukocyte count 19,600 per cubic millimeter, with 78% neutrophils, dropping to 11,600, with 79% neutrophils; operated on on 5th day in hospital, through incision in right flank; discharged from hospital 22d day
Case 6:	Youth aged 17; duration of symptoms 48 hours; temperature 101 F.; pulse rate 120; leukocyte count 10,700 per cubic millimeter, with 84% neutrophils; patient looked sick; dextrose and saline or distilled water with daily chloride determinations; pantopon (a mixture of hydrochlorides of opium alkaloids) given liberally; Wangenstein suction continuously for 16 days; 3 blood transfusions; palpable mass in the right lower quadrant formed and then resolved; discharged 34th day in hospital; has been followed since but has refused operation to date
Case 7:	Woman aged 62; ill 5 days; temperature 100.3 F.; pulse rate 80 on admission; leukocyte count 13,800 per cubic millimeter, with 78% neutrophils; next day 16,800, with 82% neutrophils, and the following day 19,800, with 74% neutrophils; temperature had risen to 104 F.; pulse still 80; Ochsner treatment had been advised and instituted but in the presence of rising fever and leukocyte count operation was undertaken; abscess mass found; this was opened, suctioned out and drainage instituted; temperature went to 105 F.; patient died on the 5th postoperative day

Number  
of Cases  
7

Deaths  
2

Mortality,  
Percentage  
28.5

rate ranging from 120 to 160. Generalized abdominal distention was present in 9 of these. Operation was followed by death in 3 cases in twenty-four hours, in 2 within forty-eight hours and in 2 within seventy-two hours.

During the period from 1935 to 1938, of the 13 patients who died there were 8 subjected to immediate operation despite the presence of high fever and a high pulse rate. Three had generalized abdominal distention. One died in twenty-four hours and 1 within seventy-two hours.

Twenty-one of these 46 patients who were immediately operated on in the presence of reactions labeling them as acutely ill had a perforated appendix or beginning abscess formation.

It is possible, as will be shown in a later table, preoperatively to conceive that rupture has taken place, and delay undertaken to prepare the patient for operation should therefore carry no onus. It is known that many patients when put to bed in the hospital and given parenteral or intravenous fluids and a Wangenstein type of duodenal suction to reduce the abdominal distention will show a decided improvement. Operation can then be undertaken at such time as this improvement is noted. The delay may be only for a few hours; it may then prove that an Ochsner regimen is the treatment of choice, and operation may be done on localization of an abscess or after full recovery.

Since this work was started, Dr. Thew Wright,<sup>12</sup> of Buffalo, has read a paper before the Monroe County Medical Society (March 21, 1939) on the treatment of diffuse peritonitis, in which he showed a great reduction in the mortality rate when this type of procedure was adopted.

As 1 case was hopeless from the start and a true Ochsner regimen was not followed in case 7, those cases in which the delayed treatment was actually used numbered 5, without a death. It therefore may be said that delayed treatment in the delayed case has a place in the surgeon's armamentarium and in selected cases will be a factor in a lowered death rate from acute appendicitis.

#### BACTERIAL FLORA IN ACUTE APPENDICITIS

Only 49 cultures were made of the abdominal fluid at operation for acute appendicitis in the period from 1930 to 1934. In the report for this period, published in 1935, it was recommended that culture be made a routine, as it was thought that the bacteriologic picture might be a factor in the mortality rate from appendicitis. The disease had been thought to be more prevalent since the influenza epidemic of 1918 and to occur more frequently during the months in which infections of the upper respiratory tract were prevalent. The observation has been made during analysis of these cases (from charts not accepted for this study) that several patients are always operated on in this yearly season who prove not to have acute appendicitis but an abdominal manifestation of acute disease of the upper respiratory tract itself or pneumococcic or streptococcic peritonitis.

The cases in the ward service in the past four years have furnished additional information as to bacteriology. Surgeons operating on the

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12. Wright, T.: The Treatment of Diffuse Peritonitis, *Bull. M. Soc. County of Monroe* 6:82-88, 1939. Wright, T.; Aaron, A. H.; Regan, J. S., and Milch, E.: The Management of Patients with Diffuse Peritonitis, *J. A. M. A.* 113:1285-1288 (Sept. 30) 1939.

private patients are not as prone to make cultures. Of the 725 cases material for culture was taken at operation in 169.

The data for the two periods are given in table 30.

Unfortunately, cultures were not made in all of the cases in this period in which death occurred. However, the great prevalence of *B. coli* and the staphylococcus was noted, and the majority of deaths occurred in the presence of these organisms. They occurred alone or combined in 79 cases; 7 of the deaths occurred in this group. In the case of the eighth patient who died there was a single culture of nonhemolytic streptococcus. Altmeier,<sup>13</sup> of Detroit, concluded that neither *B. coli* nor the streptococcus is often cultured alone and that no deaths occur

TABLE 30—*Bacteriologic Data*

Bacterial Flora	1930 1934		1935 1938	
	Number of Cases	Deaths	Number of Cases	Deaths
Staphylococcus; streptococcus, <i>Bacillus coli</i>	1	1	10	0
<i>B. coli</i> and Staphylococcus	12	1	33	.
<i>B. coli</i> .....	1	0	1	1
<i>B. coli</i> and <i>Bacillus welchii</i> .. ..	2	1	0	0
Staphylococcus and nonhemolytic streptococcus	6	0	1	0
Staphylococcus	5	0	14	1
<i>B. coli</i> and hemolytic streptococcus	1	0		
Nonhemolytic streptococcus .. . . .	5	1		
<i>B. coli</i> ; Streptococcus; <i>Bacillus proteus</i> .	0	0	2	0
<i>B. coli</i> ; Staphylococcus, <i>B. proteus</i>	0	0	1	0
Hemolytic streptococcus	0	0	3	0
<i>B. proteus</i> .. . . .	0	0	1	0
<i>B. coli</i> and nonhemolytic streptococcus .	0	0	8	0
Staphylococcus and hemolytic streptococcus	0	0	1	0
Sterile cultures	16	0	82	0
Total	49		169	

when one bacterium is recovered. His *Bacterium melanogenicum*, which he isolated in 92.7 per cent of all cases, is, of course, new, and I have had no experience with its isolation here, but cultures showed a rather high incidence of single organisms, and deaths have occurred under these conditions in this series. I agree that no prognosis can be made from the bacterial flora in cases of appendicitis.

#### SURGICAL TREATMENT OF THE APPENDIX FOR PRIVATE AND WARD PATIENTS

An analysis of ward and private surgical treatments in cases of acute appendicitis was done for two reasons. The first was to discover whether more patients were admitted with the advanced type of the disease in the ward service than in the private, and the second was to see whether

13 Altmeier, M. A. Bacterial Flora of Acute Perforated Appendicitis with Peritonitis, *Ann Surg* 107:512-518, 1938

the house surgeons incurred a mortality rate that varied from that noted by the surgeons operating on the private patients. These data are shown in table 31.

TABLE 31.—*Comparison of Ward and Private Patients*

Ward Patients	Abscess		Perforation		Gangrene		Acute Appendicitis	
	Number of Cases	Deaths	Number of Cases	Deaths	Number of Cases	Deaths	Number of Cases	Deaths
1935.....	9	1	8	2*	10	0	21	0
1936.....	9	1	6	0	4	0	48	0
1937.....	5	3**	6	0	12	0	35	0
1938.....	3	0	8	0	5	0	39	0
Totals...	26	5 19.2%	28	2 7.11%	31	0 0%	143	0 0%
Private Patients								
1935.....	7	2	5	1	21	1	61	0
1936.....	4	0	12	0	10	1	93	0
1937.....	4	1	13	0	16	0	103	0
1938.....	5	0	10	0	13	0	113	0
Totals...	20	3 15%	40	1 2.5%	60	2 6.6%	370	0 0%

\* Two not operated on.

\*\* One not operated on. One operated on by attending surgeon.

TABLE 32.—*Cases of Early Involvement*

Case 1:	Man 24 years of age; ill 12 hours before admission; leukocyte count 11,030 per cubic millimeter, with 72% neutrophils; observed 24 hours in hospital; leukocyte count 14,500, with 82% neutrophils; temperature to 99 F.; gangrenous appendix removed; recovered
Case 2:	Man aged 22; ill 24 hours; observed 24 hours; acute appendicitis; appendix removed; leukocyte count 9,500 per cubic millimeter, with 60% neutrophils; temperature 99.2 F.; recovered
Case 3:	Woman aged 23; ill 24 hours; observed 24 hours for salpingitis; leukocyte count 19,400 per cubic millimeter, with 81% neutrophils; acute appendicitis; appendix removed; recovered
Case 4:	Man aged 21; ill 5 hours; leukocyte count 10,350 per cubic millimeter, with 65% neutrophils; temperature 100 F.; delayed 24 hours because of low count; acute appendicitis; appendix removed; recovered
Case 5:	Man aged 30; ill 14 hours; leukocyte count 16,200 per cubic millimeter, with 85% neutrophils; at end of 24 hours, 17,000, with 80% neutrophils; temperature 99.2 F.; acute appendicitis; appendix removed; recovered
Case 6:	Woman aged 53; ill only 6 hours; leukocyte count 15,850 per cubic millimeter, with 87% neutrophils; at end of 24 hours, 25,450, with 83% neutrophils; temperature 101.2 F.; diagnosis, acute cholecystitis; perforated appendix found at operation; in hospital 40 days
Case 7:	Woman aged 41; symptoms 48 hours; leukocyte count 12,400 per cubic millimeter, with 88% neutrophils; temperature 100.3 F.; at end of 24 hours, leukocyte count 18,500, with 88% neutrophils; exploration; midline incision; gangrenous appendix removed; recovered in 16 days
Case 8:	Man aged 45; ill 48 hours; studied 24 hours after admission; leukocyte count 8,700 per cubic millimeter, with 82% neutrophils; rose to 15,400, with 82% neutrophils; temperature 102 F.; gangrenous appendix
Case 9:	Man aged 68; ill 72 hours; temperature normal; leukocyte count 14,400 per cubic millimeter, with 84% neutrophils; studied by barium sulfate clysmas for obstruction; temperature at 24 hours, 102.1 F.; leukocyte count dropped to 7,800, with 76% neutrophils; exploratory operation; left rectus incision; ruptured appendix; died fourth post-operative day

This table shows that 37.2 per cent of the ward patients had the advanced type of acute appendicitis and that only 24.4 per cent of the private patients were admitted at this stage. The mortality rate for

the ward patients was 3.07 per cent and for the private patients 1.22 per cent. This coincides with the observation (table 14) that a percentage of advanced conditions, approaching 35, carry with them a mortality rate of at least  $33\frac{1}{3}$  per cent more than when the percentage of advanced conditions approximates 25.

Further analysis, however, should show a corrected operative rate, as 1 ward patient was admitted in a moribund condition and died without operative intervention; 1 was treated for peritonitis from a septic condi-

TABLE 33—*Cases of Late Involvement*


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Case 1:	Woman aged 53; symptoms 4 days before admission; temperature 101.4 F.; leukocyte count 7,400 per cubic millimeter, with 64% neutrophils; studied for 24 hours without preparation; coarse rales in both pulmonary bases and question of malignancy of mass in right lower abdominal quadrant; exploration; paramedian incision; appendiceal mass found; incision closed; simple drainage of abscess without attempt to remove or find appendix; recovered 32d day in hospital
Case 2:	Woman aged 57; ill for 10 days and observed for six more days in hospital for acute nephritis; temperature had been subsiding to normal; leukocyte count 17,000 per cubic millimeter, with 82% neutrophils; operation through McBurney incision with attempt to remove appendix in presence of large abscess; temperature immediately after operation to 105 F.; general peritonitis, with death on 17th day
Case 3:	Woman aged 28; symptoms 9 days before admission; treated for peritonitis from septic abortion; died 49th day in hospital; autopsy; ruptured appendix and pyelo phlebitis
Case 4:	Man aged 43; ill 6 days at home; leukocyte count 14,600 per cubic millimeter, with 62% neutrophils; temperature 101 F.; studied 24 hours; abdomen explored through right rectus incision; appendiceal abscess found; incision closed; appendix removed via McBurney incision; recovery in 21 days
Case 5:	Woman aged 31; under treatment at home for acute pelvic infection with subsiding temperature for 2 weeks; acute flare up sent the patient to the hospital, with observation for 2 days; leukocyte count 13,300 per cubic millimeter, with 64% neutrophils; temperature normal; exploration with midline incision; surgical report described appendix as perforated and in mass with right tube and ovary; recovery
Case 6:	Woman aged 54, ill 48 hours at home, leukocyte count on admission 17,400 per cubic millimeter, with 92% neutrophils; observed in hospital 18 days for pelvic abscess; leukocyte count then 21,800 per cubic millimeter, with 88% neutrophils; temperature 100 F.; diagnostic dilation and curettage, followed by exploratory laparotomy through midline incision, no pathologic change found in uterus; abscess discovered and drained; temperature immediately rose to 105 F., and death occurred on the 12th postoperative day; autopsy revealed ruptured appendix
Case 7:	Man aged 51; ill six days at home; leukocyte count stayed at 10,000 per cubic millimeter, with 62% neutrophils; temperature normal until slight rise to 99 F. on sixth day in hospital, when exploratory celiotomy was done; appendicitis suspected after observation for a genitourinary condition; McBurney incision used; simple drainage of an appendiceal abscess; appendix sloughed except for tip in wall of abscess; this was left in; recovery (20th day)

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tion following abortion and proved at autopsy to have a perforated appendix; 1 was admitted after two operations at another hospital, and on admission no treatment was deemed feasible. Autopsy showed cecal fistula and iliopsoas abscess. Treatment in 1 case was delayed for diagnosis for eighteen days, the delay being followed by an exploratory operation which revealed an abscess. Autopsy proved rupture of the appendix. The responsibility in such a case rests on the attending staff. A corrected rate for the house staff, then, would be 1.31 per cent, which is equivalent to the rate for the private surgeons.

#### NEED OF EARLY DIAGNOSIS OF ACUTE APPENDICITIS

The last factor to be brought out of the study of these cases is that the result depends entirely on early diagnosis. This factor is observed

with those patients who present themselves with a problem of pathologic change in the right lower quadrant. Diagnosis is sometimes delayed for various procedures, some of which are harmful to an inflamed appendix, such as administration of barium sulfate by mouth or of barium sulfate enemas in the course of gastrointestinal roentgen study.

The delay incurred may allow rupture in the case of early appendicitis, and in the late stages an exploration is usually done through an incision unsuitable to removal of the appendix or such that protective barriers are broken and surgically spread peritonitis results. Data are given in table 32.

Of the 9 cases, the appendix in 5 had been allowed to perforate or become gangrenous, resulting in many increased days in the hospital if recovery occurred and in death in 1 instance.

In these groups, then, 4 deaths occurred, representing 30.7 per cent of the mortality in the past four years. For the 16 cases in which treatment was delayed for diagnosis the mortality rate was 25 per cent. This would certainly give rise to the observation that physicians perhaps have forgotten the old teaching that 85 per cent of the pathologic process in acute conditions of the abdomen may be found in the appendix and that if there is the slightest indication to suspect the appendix an operation, even if the appendix proves to be uninvolved, should carry no embarrassment, censure or mortality, whereas the policy of watchful waiting may carry all of these.

#### DETERMINATION OF STAGE OF ACUTE APPENDICITIS: A WORKABLE TABLE

In studying the results of delay as it affected the physical and economic status of the patient with acute appendicitis, it was found that the table prepared (table 34) can be used by the surgeon as a workable basis on which he may reasonably form a conception of the stage of the disease and anticipate his treatment of the patient from the bedside consultation. It will also serve the physician who must persuade the reluctant patient when operation is advised, as many who would refuse surgical treatment on a physical basis alone will accept it when proof is offered that delay involves greater economic and financial loss.

There are, of course, occasional cases of atypical appendicitis, but in many of these the condition is due to the transportation necessary and, as Bower pointed out, to a silent phase of the disease. It is recommended that the temperature, pulse rate and condition of the abdomen as noted by the family physician at the house be incorporated with the history and other data at the hospital. This inclusion will frequently prevent a delay in diagnosis until further cardinal signs return.

Table 34 is based on a study of 648 cases observed in this hospital in the past four years. It shows that in this comparatively large series the average patient with acute uncomplicated appendicitis has reached the surgeon's care in twenty-seven and eight-tenths hours. His temperature is 99.4 F.; the pulse rate is 94.8; the leukocyte count averages 15,660 per cubic millimeter, with 82.4 per cent neutrophils. If operated on immediately, he will spend only an average of nine and one-half days in the hospital. Secondary peritoneal abscess occurs in only 1 of 23 such patients. Culture of the peritoneal fluid shows it to be sterile in 3 of 4. A delay of forty-two and one-third hours shows an appendix that will be gangrenous on the average. The patient has a temperature of 100.3 F.; the pulse rate is 97.7, with the leukocyte count rising to 17,993, with 84.9 per cent neutrophils. One of 30 of these patients will die. If recovery takes place it will be after an average of eleven and eight-

TABLE 34.—*Table for Determination of Stage of Disease*

	Type of Appendicitis			
	Acute	Gangrenous	Perforating	Abscess
Delay, hours.....	27.8	42.3	45.3	98.8
Temperature.....	99.4	100.3	101.0	101.0
Pulse rate.....	94.8	97.7	105.0	101.0
Leukocyte count and neutrophils	15,662—82.5%	17,993—84.9%	17,911—85.8%	18,580—83.2%
Abscess.....	1:23	1:9	1:3	1:4
Culture.....	1 pos.; 3 neg.	1 pos. to 1 neg.	8 pos. to 1 neg.	All pos.
Days in hospital.....	9.5	11.8	22.1	22.8
Mortality.....	0	1 in 30	1 in 13.3	1 in 6

tenths days in the hospital. The chances of secondary abscess formation are 1 in 9. Cultures are sterile in only 50 per cent of the cases. Perforation, on the average, has occurred only three and three-tenths hours later, the patients being admitted in forty-five and three-tenths hours. The temperature has risen to 101 F. and the pulse rate to 105. The average leukocyte count is 17,911 per cubic millimeter, with 85.8 per cent neutrophils. The chances of survival are only 12 in 13; recovery, if it takes place, occurs after twenty-two and one-tenth days. In 1 of 3 cases secondary abscesses will occur. Sterile cultures are obtained in only 1 of 9 cases.

A delay of ninety-eight and eight-tenths hours usually results in abscess formation. The temperature is 101.5 F. and the pulse rate 101.5. The leukocyte count is higher, averaging 18,580 cubic millimeters, with 83.2 per cent neutrophils. The chances of survival have been lowered to 5 in 6, and the average stay in the hospital is twenty-two and eight-tenths days. Secondary peritoneal abscesses occur in 1 of 4 cases, and cultures yield bacteria in every instance.



BLOOD PICTURE IN CASES OF ACUTE APPENDICITIS AS RELATED  
TO MORTALITY AND TREATMENT

Further investigation of the blood count along these lines produced a table which, in a diagnostic way, presents a fairly accurate picture of what one may find on opening the abdomen. A leukocyte count under 10,000 per cubic millimeter was noted in only 48 of these cases. Of these, 41 were examples of the acute inflammatory stage only. In 7 the condition was further advanced. In 4 the appendixes were gangrenous and in 3 they were perforated. A leukocyte count ranging from 10,000 to 15,000 per cubic millimeter was shown to occur in 220 cases. In 161 the condition was in the acute stage; in 25 it was gangrenous; in 19 there was perforation, and in 15 there was abscess formation. There were 180 patients with leukocyte counts ranging from 16,000 to 20,000 per cubic millimeter. Of these, 3 had only acute appendicitis; 35 showed

TABLE 35.—*Data on Leukocyte Counts*

	Leukocyte Count in Thousands per Cubic Millimeter				
	5 to 10	10 to 15	16 to 20	21 to 30	31 to 33
Number of cases.....	48	220	180	67	3
Abscess.....	0	15	12	12	0
Ratio.....	0	1:14.5	1:15	1:5	0
Perforation.....	3	19	22	13	1
Ratio.....	1:16	1:12	1:8	1:5	...
Gangrene.....	4	25	35	16	2
Ratio.....	1:12	1:5	1:5	1:2	...
Acute appendicitis.....	41	161	111	26	0
Ratio of advanced cases...	1 in 7	1 in 4	1 in 2.5	1 in 1.6	All pos.
Mortality, percentage.....	0	2.7	2.2	3.0	33.3

gangrenous changes; 22 had perforated appendixes, and 12 showed abscess formation. In the group with the count from 21,000 to 39,000 per cubic millimeter, which numbered 67 patients, 26 had only acute appendicitis; 16 had labeled gangrenous conditions; 13 had perforated appendixes, and 12 had local abscesses. There were 3 with leukocyte counts over 30,000 per cubic millimeter; 2 had gangrenous appendicitis and 1 a perforated appendix. These data are given in table 35.

This would indicate that the higher the leukocyte counts, the greater percentage of advanced conditions will be found at operation. It would indicate also that, although 6 deaths occurred in the group with leukocyte counts between 10,000 and 15,000 per cubic millimeter and 4 deaths in the group with leukocyte counts from 15,000 to 20,000 per cubic millimeter, the actual percentage of mortality increased with the higher leukocytic levels.

The work of Wright<sup>12</sup> is again referred to, as he pointed out that in his series, leukopenia was noticed on the fourth and the fifth day. This observation coupled with a falling blood pressure was to him a warning

that blood transfusion was immediately needed. With 9 of the patients in this series who died, a drop in the leukocyte count was noticed after leukocytosis. Transfusion had been used for 3 of these without influencing the outcome. Wright advocated daily blood counts and blood pressure readings as therapeutic aids. In this series blood pressure readings have hardly ever been used, and in the case of the private patients even blood counts taken on admission were woefully lacking. Postoperative blood counts were taken in only a few instances. In the light of this newer study, it is recommended that for the patient with complicated appendicitis these procedures be made a routine postoperative order.

#### SUMMARY

Reports from various authors and clinics place the mortality rate from acute appendicitis from 2.16 per cent to 8.5 per cent. Since 1930, with 133 proved cases of acute appendicitis and a rate of 6.01 per cent, the number of cases in this hospital has increased 25 per cent, and the mortality rate has decreased yearly (table 5) until 1938, in which year there were 199 cases, with a death rate of only 0.5 per cent. This is a record of which any hospital may well be proud.

An attempt has been made by reporting this series of cases to show some factors that have contributed to this reduced rate. In studying these factors, some were found that seem to point to a further reduction to be obtained by attention to certain principles, which may be summed up as follows: 1. Continued education of the public against delay in the presence of abdominal upsets. 2. Continual education of physicians and surgeons to keep them appendicitis conscious, so that early diagnosis may be made and operation undertaken in the first twelve hours. This is particularly necessary for patients under 10 years of age and over 40, in whose cases "watchful waiting" has apparently been the general policy and has proved to have disastrous results. 3. Preoperative preparation of the patient who is acutely ill, with high fever, a high pulse rate, dehydration and shock. 4. A well conceived preoperative plan of treatment by the surgeon, which includes evaluation of the stage of appendicitis, so that he may correctly decide between immediate operative intervention and delay and also on the choice of an anesthetic, the proper incision and the limitations of surgical intervention. The postoperative care should be such as to anticipate further involvement and make use of those procedures which will aid in combating this. These are attention to fluid balance, use of the duodenal tube to combat nausea, vomiting and distention and avoidance of increasing these symptoms by administration of fluid or food by mouth or of futile enemas before restoration of bowel tone. Morphine in sufficient amounts to produce its physiologic action is to be given, and, lastly,

the patient's condition can apparently be gaged by daily leukocyte counts and frequent blood pressure readings. In the presence of a marked drop, transfusion is essential.

#### CONCLUSIONS

An analysis of 2,013 cases of acute appendicitis is presented. The analysis was made to ascertain the mortality rate in a general hospital and the factors contributing to that rate. The cases included were proved cases occurring in the period from 1925 through 1938, which has been divided into two five year periods and one four year period for comparison.

The incidence of operation for acute appendicitis has increased 25 per cent, and the mortality rate has decreased 50 per cent.

Sex ratio, age incidence, anesthesia and history of catharsis have remained the same in the three periods, as has the factor of delay in reaching the surgeon's care. Preoperative preparation of the patient has not been done, and immediate operation has been the rule in all periods.

The factors credited with the reduced mortality rate are: (1) better postoperative care of the patient; (2) use of the McBurney incision, and (3) closure of all wounds except in cases of well walled-off abscess.

A small series of cases in which the delayed, or Ochsner, treatment has been used seems to show that this treatment has a place in the armamentarium of the surgeon.

A table is presented which seems to allow the surgeon to evaluate preoperatively the stage of the disease and thereby to permit a well planned regimen of treatment throughout.

# CYTOLOGY OF THE GASTRIC CONTENTS, WITH SPECIAL REFERENCE TO GASTRITIS

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Serious students of gastric surgery and gastroenterology are cognizant of the fact that there has been a recent revival of interest in cytologic examination of the gastric juice, especially with respect to gastritis. Naturally one wonders about the rationale of this procedure as a diagnostic measure, for, with the possible exception of microscopic study of the bile and the duodenal content after biliary drainage, such a procedure is not routinely used in the diagnosis of other lesions of the digestive tract or of mucosal lesions in organs more accessible than the stomach. However, modifications of such a method are used in clinical medicine. For example, in the diagnosis of cystitis the presence of pus cells in the urine is significant, just as the presence of numerous eosinophils in mucus or tissues is important in the diagnosis of allergic states. But since epithelial desquamation, as well as exudation, is characteristic of mucosal inflammation, it seems reasonable to conclude that cytologic examination of the gastric juice under favorable conditions is of diagnostic value in cases of gastritis.

The procedure also promises to be an important adjunct to roentgenoscopic and gastroscopic examination and to be helpful in determining the effect of treatment of gastritis. Additional data concerning the effects of noxious agents or disease processes other than gastritis on the gastric mucosa may be obtained in this way, as Westphal and Weselmann<sup>1</sup> recently demonstrated in their study of the effect of excessive cigaret smoking (*Cigaretten Gastritis*).

In a previous study by one of us (R. E. M.<sup>2</sup>) on the histologic structure of the gastric mucosa, numerous clumps of cells within the lumens of the gastric crypts were noted. Figure 1 shows an example

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From the Division of Medicine, the Mayo Clinic.

1. Westphal, K., and Weselmann, H.: Ueber Nikotinschädigungen des Magens, Deutsche med. Wchnschr. 65:1189-1192 (July 28) 1939.

2. Mulrooney, R. E.: A Histological Study of the Mucosa of Normal Stomachs with Immediate Fixation After Death, Thesis, University of Minnesota Graduate School, 1935.

of this. These accumulations of cells were seen in the normal gastric mucosa as well as in the inflamed mucosa. They were, however, much more numerous in the latter. It seemed reasonable, therefore, to expect that a diagnosis of gastritis might be determined by a cytologic study of the gastric contents.

According to Vogels,<sup>3</sup> Rosenbach, in 1882, was one of the earliest workers to attempt to recognize parts of ulcers by a microscopic study of the cells in the gastric contents. Jaworski<sup>4</sup> in 1886 and 1887 attempted to differentiate between normal and pathologic cell contents. He also mentioned fermentative destruction of the cytoplasm of the

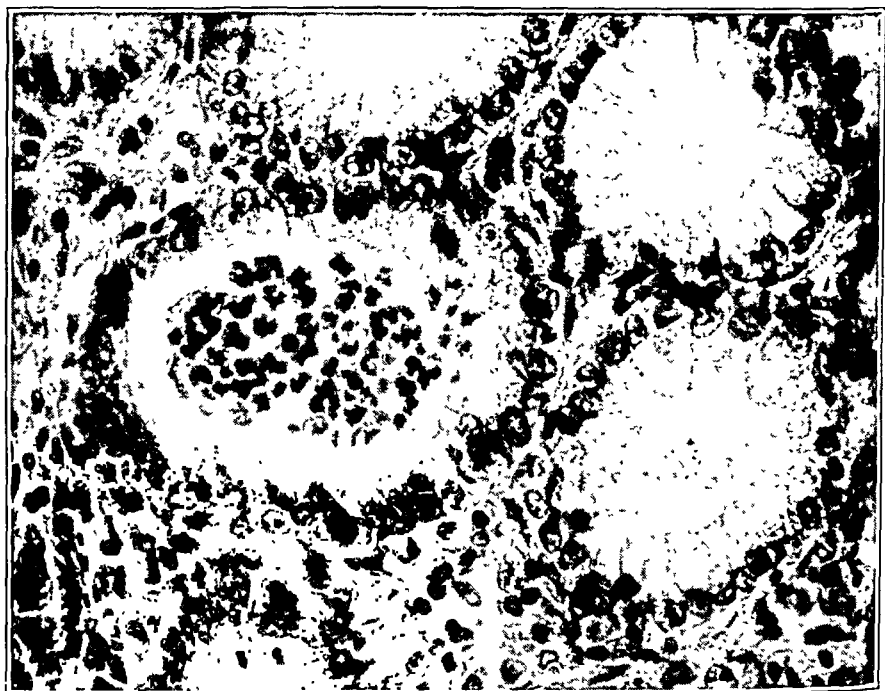


Fig. 1.—Antrum, greater curvature ( $\times 450$ ). Note the gland filled with cells, which are predominantly leukocytes. Note also the absence of evidence of inflammation either in the surrounding glands or in the connective tissue.

3. Vogels, C.: Die Bewertung der Zellbestandteile (Cytodiagnostik) im Ausgeheberten nach Alkoholprobetrunk bei Magen- und Duodenalerkrankungen. Die Oxydasereaktion als diagnostisches Hilfsmittel, *Deutsche Ztschr. f. Chir.* **240**: 601-613, 1933.

4. Jaworski, W.: Beitrag zur klinischen Mikroskopie des Mageninhalt. *Centralbl. f. klin. Med.* **7**:849-855 (Dec.) 1886; Beobachtungen über das Schwinden der Salzsäuresecretion und den Verlauf der katarrhalischen Magenerkrankungen, *München. med. Wchnschr.* **34**:117-120 (Feb. 15) 1887; Methoden zur Bestimmung der Intensität der Pepsin-Ausscheidung aus dem menschlichen Magen und Gewinnung des natürlichen Magensaftes zu physiologisch-chemischen Versuchszwecken, *ibid.* **34**:634-637 (Aug. 16) 1887.

cells. In 1894 Boas<sup>5</sup> tried to differentiate between the cellular elements found in normal, inflammatory and ulcerative states. He was particularly interested in the diagnosis of malignant ulcers. Marini<sup>6</sup> in 1909 tried to correlate the cellular elements in the gastric contents with the cells observed in sections of the gastric mucosa.

Since the studies by Bensley,<sup>7</sup> Konjetzny,<sup>8</sup> Moszkowicz,<sup>9</sup> Orator<sup>10</sup> and many others on the histologic structure of the stomach, there has been an intensified interest in the cytologic character of the gastric juice. In 1922, 1923 and 1924 Loeper and Marchal<sup>11</sup> published the results of their exhaustive studies on the peptic function of the leukocytes in the gastric juice. Westphal and Kuckuck<sup>12</sup> in 1933 developed a technic of fractional aspiration of the gastric contents after an alcohol test meal and applied it to differential diagnosis of various pathologic conditions of the stomach. They did not, however, attempt to neutralize the gastric acids. In 1936 Pevsner and Gordon<sup>13</sup> reported a series of 500 cases of gastritis diagnosed as such by a histologic study of the sediment from the gastric contents. Monaghan, Bockus, Kornblum and

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5. Boas, I.: Zur Kenntnis der mechanischen Insufficienz des Magens, *Deutsche med. Wchnschr.* **20**:576-578 (July 12) 1894.

6. Marini, G.: Ueber die Diagnose des Magenkarzinoms auf Grund der cytologischen Untersuchung des Spülwassers; eigene Beobachtungen über den normalen und pathologischen Zelleninhalt des Magens, *Arch. f. Verdauungskr.* **15**: 251-267, 1909.

7. Bensley, R. R.: The Structure of the Mammalian Gastric Glands, *Quart. J. Micr. Sc.* **41**:361-390 (Nov.) 1898.

8. Konjetzny, G. E.: (a) Chronische Gastritis und Duodenitis als Ursache des Magenduodenalgeschwürs, *Beitr. z. path. Anat. u. z. allg. Path.* **71**:595-618, 1923; (b) Die Peckepithelveränderungen der Magenschleimhaut bei akuter Gastritis, *Virchows Arch. f. path. Anat.* **275**:816-827, 1930.

9. Moszkowicz, L.: Zur Histologie des ulcusbereiten Magens, *Arch. f. klin. Chir.* **122**:444-499, 1922-1923.

10. Orator, V.: Beiträge zur Magenpathologie, *Arch. f. klin. Chir.* **134**:663-681, 1925.

11. Loeper, M., and Marchal, G.: (a) La constance de la leucogénèse intragastrique après ingestion de bouillon, *Compt. rend. Soc. de biol.* **87**:1081-1082, 1922; (b) Le rôle de la leucogénèse intragastrique dans la digestion des albumines, *ibid.* **87**:1083-1084, 1922; (c) Action hypoleucopédétique et hypersécrétante de l'esérine, *ibid.* **91**:544-545, 1924; (d) L'épreuve de la leucopédèse gastrique dans les intoxications alimentaires d'origine protéique, *Bull. et mém. Soc. méd. d. hôp. de Paris* **2**:1219-1224 (July 27) 1923; (e) La leucopédèse gastrique, *Ann. de méd.* **14**:257-283, 1923.

12. Westphal, K., and Kuckuck, W.: Der Reizmagen: Untersuchungen über Funktion und Pathologie der Magenschleimhaut; der Zell- und Leukocytengehalt des Magensaftes unter normalen und pathologischen Bedingungen, *Ztschr. f. klin. Med.* **124**:616-652, 1933.

13. Pevsner, M., and Gordon, O.: Clinique et diétothérapie des gastrites chroniques, *Acta med. Scandinav.* **88**:278-282, 1936.

Moffitt<sup>14</sup> modified the technic of Pevsner and Gordon and reported a series of 18 cases of gastritis.

In all of the methods noted previously the cells were studied without any attempt to neutralize the gastric acids. It is well known, of course, that the gastric acids will facilitate digestion of the cells and that therefore the morphologic characteristics of the cells will be altered. In 1939 Hauth<sup>15</sup> published a technic by which he attempted to neutralize the gastric acids in vivo and thereby prevent autodigestion of the cells in the gastric juice.

The technic used in this study was a modification and combination of the technics proposed by Westphal and Kuckuck and by Hauth. The tissue technic of Monaghan and his co-workers did not appeal to us, since it did not set up definite normal standards from which variations could be evaluated. Furthermore, it was time consuming and did not involve precautions to preserve the delicate structure of the partly digested cells. By use of the combined technics of Westphal and Kuckuck and of Hauth the advantages of each were retained, while certain disadvantages of both were overcome.

The test was made on fasting stomachs. Two hundred cubic centimeters of 5 per cent alcohol was instilled into the stomach, and at ten minute intervals 10 to 15 cc. of the gastric contents was aspirated until 8 specimens had been obtained. Table 1 is an example of the work sheet of the examination of 1 patient, from which the various steps of the test may be visualized. A rough estimate of the mucus content was noted on the basis of 1 (slight) to 4 (much). The total cell count was determined by mixing 1 cc. of the gastric juice with 9 cc. of physiologic solution of sodium chloride. All but 2 cc. of this mixture was discarded, and 6 or 7 drops of methylene blue was added to the retained portion. The methylene blue aided in differentiation of the cells from any debris present. A drop of this diluted and stained gastric juice was placed on a Neubauer counting chamber, and the cells were counted in an area of 5 sq. mm. From the dilution and volume the total cell count per cubic millimeter was calculated. Counts were made from specimens 2, 4, 6 and 8.

Smears of the undiluted gastric content of these specimens were also made. These smears were stained with the ordinary Wright stain. It was noted that the cellular elements of the gastric contents take the stain more quickly than do the cells in blood smears; consequently a slightly shorter time for staining was used. Hauth made his

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14. Monaghan, J. F.; Bockus, H. L.; Kornblum, K., and Moffitt, G. R.: Gastric Secretory Behavior in Chronic Gastritis, *Am. J. Digest. Dis. & Nutrition* 3:655-666 (Nov.) 1936.

15. Hauth, W.: Die Darstellung unverdauter Zellen aus dem Magensaft, *Deutsches Arch. f. klin. Med.* 183:363-371, 1939.





In 70 per cent of our series the concentration of gastric acids had reached a peak and was subsiding within eighty minutes of instillation of the alcohol test meal; therefore, additional specimens in this portion of the examination were unnecessary. Furthermore, the stomach was infrequently empty of the test meal by the end of eighty minutes, so that if the test was prolonged a very concentrated specimen was obtained. In such concentrated specimens erratic total cell counts were noted, and this undoubtedly accounted for Vogel's lack of reliance on the total cell counts. By making the total cell counts within eighty minutes of the start of the examination, fairly uniform counts were obtained.

After the eighth specimen (eighty minutes after instillation of the test meal) the stomach was emptied and then lavaged with 50 to 100 cc. of physiologic solution of sodium chloride to remove any excess acid. Then, as Hauth suggested, the gastric acids were neutralized in vivo by instillation of an alkaline bouillon solution composed of 10 cc. of beef bouillon extract and 5 Gm. of sodium bicarbonate diluted to 150 cc. Hauth recommended instillation of only 10 cc. of this alkaline bouillon solution, but in our experience this was not adequate. If only 10 cc. was instilled and then siphoned off (not forcibly aspirated) after a ten minute interval, the first portion was usually alkaline, but the last portion was frequently acid. When 60 to 75 cc. was instilled, this difficulty was usually overcome. The patient was instructed to turn from side to side so that the alkaline solution would neutralize the acid from all portions of the stomach. After ten minutes had elapsed, the gastric contents were completely siphoned off. Another 60 to 75 cc. of the alkaline solution was instilled and after ten minutes was again siphoned off. Three specimens were so obtained. These were centrifuged at 2,500 revolutions per minute, and the supernatant fluid was discarded. The sediment was mixed with a few drops of a solution of equal parts of human blood serum and physiologic solution of sodium chloride. Smears were made from this mixture and stained with Wright's stain. Examination was made in this manner in 50 cases.

#### ELEMENTS OF THE GASTRIC CONTENTS

*Squamous Cells.*—The squamous cells, of course, are derived from the upper part of the respiratory tract and the esophagus and therefore are of no significance in the diagnosis of gastritis. They are, however, almost invariably found in smears of gastric contents. Under Wright's stain the nucleus is large, reddish and granular. The cytoplasm is resistant to autodigestion, and frequently intact cells are seen even in acid gastric juice. The bacteria often are clumped on the cytoplasm. Figure 2 *A* shows the fine granular texture of the squamous nucleus and how it compares with the leukocytic nucleus. Figure 2 *B* is a gen-

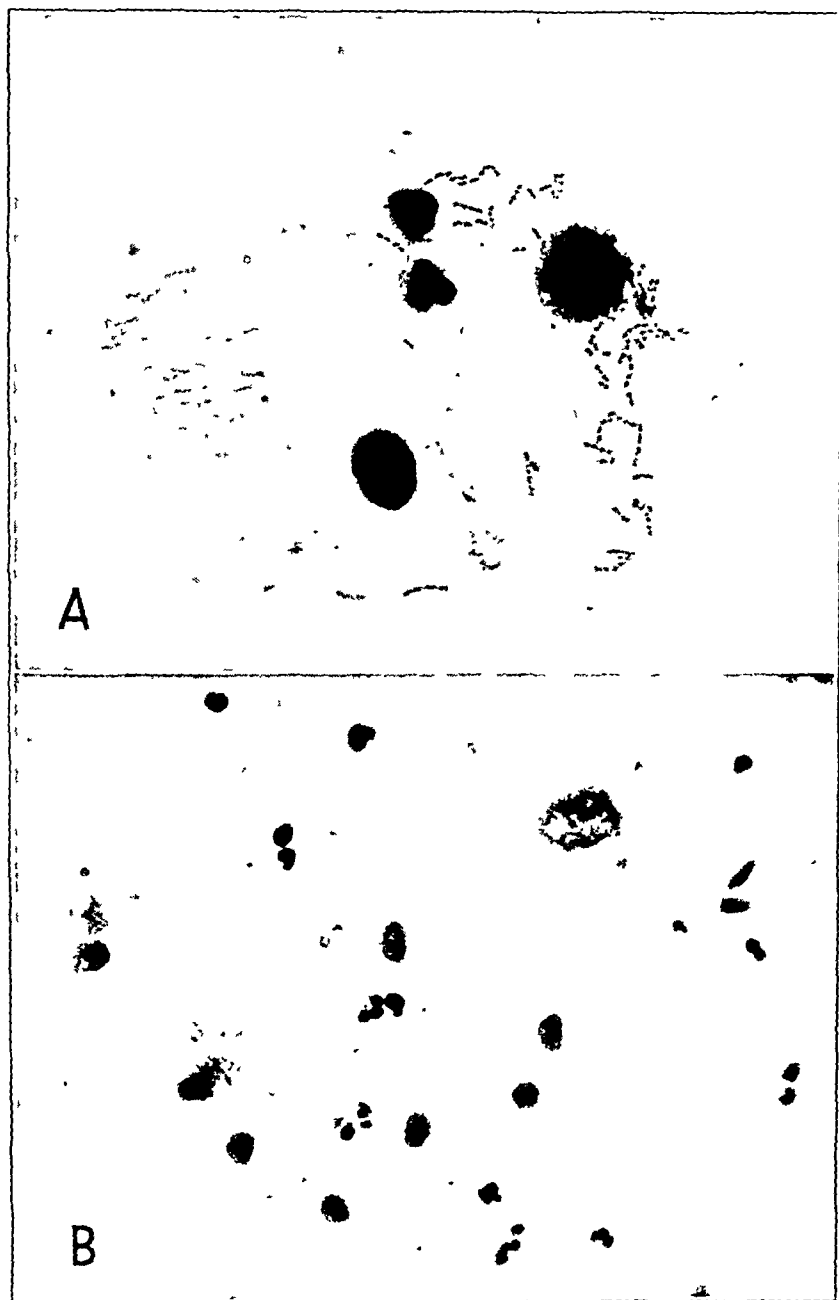


Fig. 2.—*A*, two squamous cells and two polymorphonuclear leukocytes ( $\times 950$ ). Note the relative size of the two types of cells. Note also the fine granular texture of one of the squamous cells. The gastric acids were neutralized. *B*, general view of cells without cytoplasm in acid gastric juice ( $\times 400$ ). Note the relative size of the nuclei of the epithelial, leukocytic and squamous cells. The large squamous nucleus shows its characteristic granular texture. Note that different types of nuclei can be differentiated in spite of the absence of the cytoplasm.

eral view of the cells without their cytoplasm, as seen in acid gastric juice. It will be noted that the various types of nuclei can be differentiated even though the cells have no cytoplasm.

*Epithelial Cells.*—The gastric epithelial cells appear in the gastric contents as a result of desquamation. When the gastric acids are not neutralized, the epithelial cell cytoplasm is rarely seen, since it is exceedingly susceptible to autodigestion. The epithelial nucleus is slightly larger than the leukocytic nucleus and has a fine stringy texture with occasional condensations. The size, shape and structure of the lymphocytic nucleus are not unlike those of the epithelial nucleus, so that errors between these two types of cells could arise. Bunting and

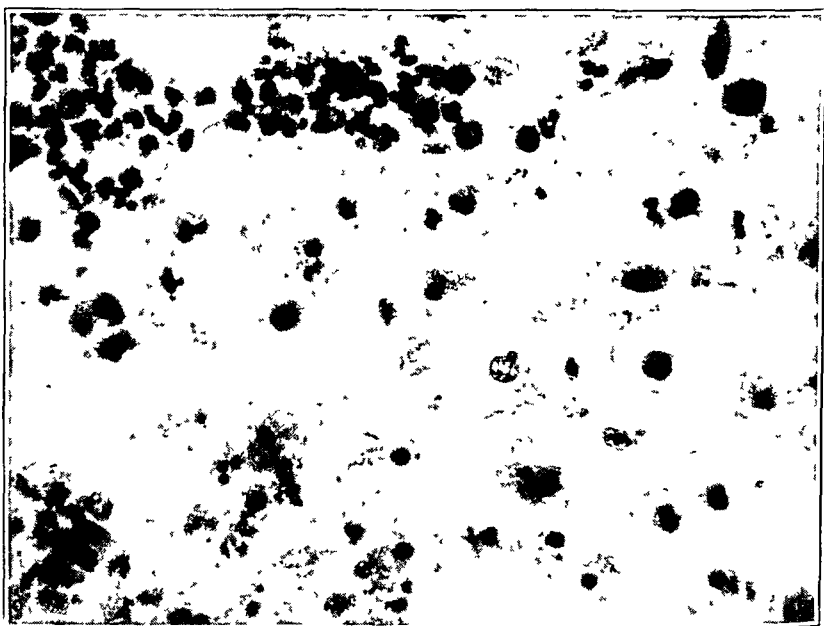


Fig. 3.—General view, showing epithelial cells and leukocytes with cytoplasm ( $\times 525$ ). Note that the cytoplasm of the cells has been preserved by neutralizing the gastric acids in vivo.

Huston<sup>17</sup> have pointed out that the number of lymphocytes in the intestinal juices is roughly proportional to the amount of lymphoid tissue in the various parts of the intestine. As the stomach has only small lymphoid follicles near the muscularis mucosae, it is not probable that lymphocytes constitute any considerable portion of the cells in the gastric contents. Figure 2B shows a comparison of the epithelial nuclei with the nuclei of leukocytes and squamous cells. Figure 3 is a general view of the cells in the gastric contents in which the gastric

17. Bunting, C. H., and Huston, J.: Fate of the Lymphocyte, J. Exper. Med. 33:593-600 (May) 1921.

acids have been neutralized. It will be noted that the cytoplasm of the epithelial cells has a fine granular texture.

*Leukocytes.*—The leukocytes, in contrast to the epithelial cells, appear in gastric contents as a result of exudation. The cytoplasm of the leukocytes is easily digested by the gastric juice, though less so than that of the epithelial cells. The characteristic lobulated appearance of the leukocytic nucleus helps to differentiate these cells even though the cytoplasm is absent. In figure 2 *B*, characteristic lobulated leukocytic nuclei are easily distinguished. Fig. 4 *A* shows nine leukocytic nuclei and one epithelial nucleus for comparison. When the gastric acids are neutralized, the cytoplasm of the leukocytes is usually in a fairly intact state. Figure 4 *B* shows how numerous these intact leukocytes may become. The specific granules of the leukocytes can often be easily seen. According to Hauth, some of the German investigators attribute an especial significance to the presence of eosinophilic leukocytes for the diagnosis of chronic gastritis, while others believe that these eosinophil-like cells are not even leukocytes but are only fragments of the reddish squamous nuclei. In this study a fair number of unmistakable eosinophils were seen, but no especial significance could be attached to their presence. No attempt to differentiate the various types of leukocytes was made, since frequently characteristic leukocytic nuclei were noted, but the cytoplasm, with its specific granules, was absent.

The exact site of the exudation of leukocytes is still debatable. Isaacs and Danielian<sup>18</sup> have shown that saliva normally contains a certain number of leukocytes. Loeper and Marchal<sup>11c</sup> stated that they saw numerous leukocytes about the capillaries near the muscularis mucosae of the stomach in dogs during digestion. Konjetzny,<sup>8b</sup> on the other hand, stated that he rarely noted any leukocytes in the connective tissue of the stomach in the absence of gastritis. Westermann<sup>10a</sup> postulated a minute break or erosion in the surface epithelium of the stomach through which the leukocytes poured into the lumen of the stomach. In a previous study by one of us (R. E. M.) on the histologic structure of the stomach, the predominant site for accumulation of leukocytes, of which figure 1 shows an example, was in the crypts of the gastric glands. Near the epithelium lining the crypts, capillaries were encountered in which leukocytes were margined. Figure 5 illustrates the leukocytes in the capillaries at the crypts prior to their migration into the lumen of the crypts. This appeared entirely independent of any gastritis and hence represented normal cellular exudation. From the crypts the leukocytes may wander into the lumen of

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18. Isaacs, R., and Danielian, A. C.: Maintenance of Leukocyte Level and Changes During Irradiation: A Study of the White Blood Corpuscles Appearing in the Saliva and Their Relation to Those in the Blood. *Am. J. M. Sc.* **174**:70-87 (July) 1927.

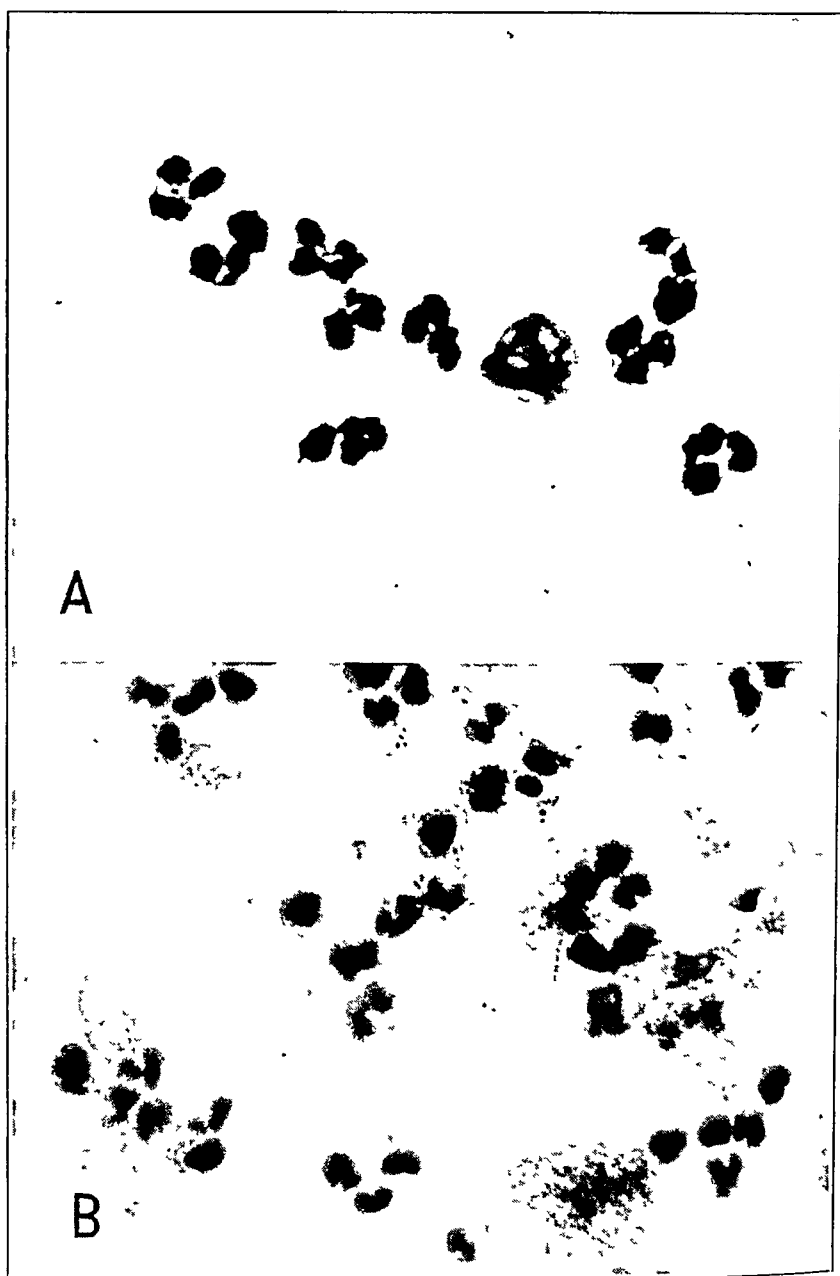


Fig. 4.—*A*, nine polymorphonuclear leukocytes and one epithelial nucleus ( $\times 900$ ). Note the relative size of the two types of nuclei shown. Note also that in spite of the absence of cytoplasm the nuclei are easily differentiated. The gastric acids had not been neutralized. *B*, general view, showing leukocytes with cytoplasm ( $\times 900$ ). Note the predominance of the polymorphonuclear leukocytes. The cytoplasm had been preserved by neutralizing the gastric acids.

the stomach as single cells or in the form of plugs. Figure 6 shows an example of a cellular plug.

*Mucus.*—Mahlo<sup>19</sup> attached great significance to the mucus of the gastric contents both in the diagnosis and in the causation of gastritis. In this study, however, no definite correlation between the degree of gastritis and the amount of mucus in the gastric content could be made.

*Bacteria.*—The only consistent increase in the bacterial flora of the gastric contents was noted in cases of gastric carcinoma. No definite correlation between the bacterial flora and the degree of gastritis present could be established.

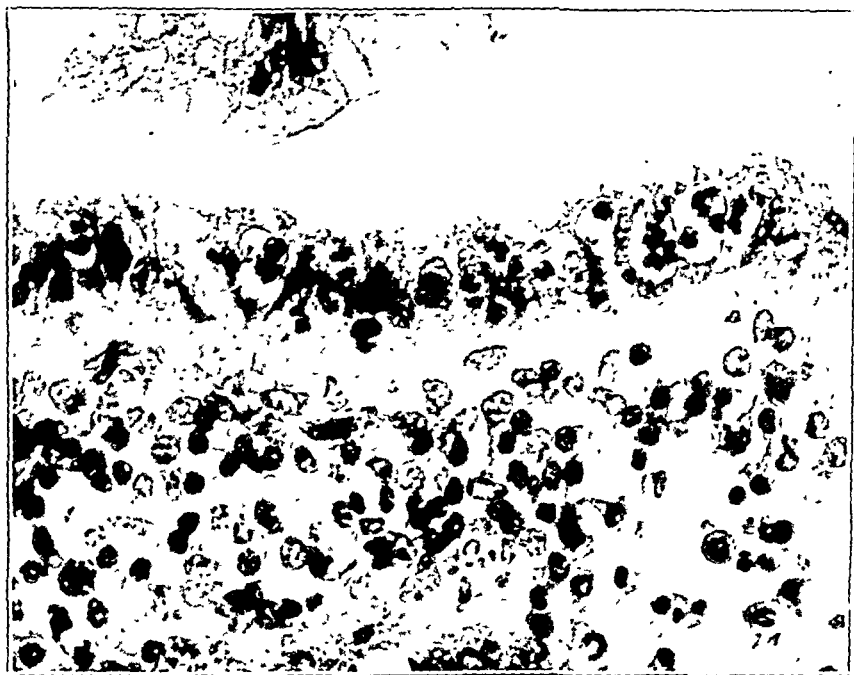


Fig. 5.—Crypt of gastric gland in fundus ( $\times 450$ ). Note the margination of the leukocytes in the capillaries preliminary to their migration into the lumen of the crypt of the gastric gland. Note also the absence of any leukocytic infiltration in the subepithelial layers.

*Parasites.*—In 1 case in which gastroduodenostomy had been done, numerous parasites of the "*Giardia lamblia*" type were seen. The nucleus of these parasites stained bright red with Wright's stain.

#### CLINICAL STUDY

Table 2 is a summary of the results of tests of 50 patients.

19. Mahlo, A.: Beziehungen zwischen der Entstehung der Gastritis und dem Magenschleim, Deutsche med. Wchnschr. **62**:1216-1218 (July 24) 1936; Kritisches zur Gastroskopie, Klin. Wchnschr. **16**:233-235 (Feb. 13) 1937.

*Normal Group.*—For a group of patients with normal stomachs, 11 were selected who were relatively young and who presented no digestive disturbances. Their ages varied from 18 to 39 years. No patients in the later decades of life were selected, because of the possibility of encountering latent or definite gastritis. According to Kauffmann<sup>20</sup> and Konjetzny,<sup>8a</sup> secondary gastritis may arise from repeated infections elsewhere in the body, and hence elderly patients would be more likely to show abnormal variations. Westphal and Kuckuck examined a small



Fig. 6.—Gastric crypt plug ( $\times 465$ ). Note the triangular shape, corresponding to the shape of the gastric crypts. Note also the greater degree of autodigestion of the cells on the surface of the plug which is exposed to the entire gastric juice.

group of patients 50 to 55 years of age but did not find any appreciable difference from the younger age groups. It will be noted that the normal average total cell count was 232 per cubic millimeter, with a range of 80 to 530. This agreed well with Westermann's<sup>16a</sup> average of 234 cells per cubic millimeter and Westphal and Kuckuck's range of 0 to 500 cells. The leukocytes averaged 16 per cent with a range of.

20. Kauffmann, F.: Experimentelle zur Gastritisfrage, Deutsche med. Wchnschr. 2:1745-1746 (Oct. 18) 1929.

11 to 21 per cent. This, likewise, approximated the results obtained by Westphal and Kuckuck and by Westermann.<sup>10b</sup>

*Duodenal Ulcer.*—Six cases of uncomplicated duodenal ulcer were studied. It will be noted from table 2 that the total cell count and leukocyte percentage fell well within the normal range. This method of study would indicate that gastritis is not an important factor in the production of duodenal ulcer. Five cases of duodenal ulcer with partial stenosis were studied. The average total cell count of 1,040 per cubic millimeter, with a range of 510 to 2,370 cells per cubic millimeter, was definitely elevated. The leukocytes were also increased to an average of 33 per cent, with a range of 29 to 37 per cent. Thus, stasis of the gastric contents appeared to be a definite factor in the production of gastritis.

TABLE 2.—*Summary of Cytologic Characteristics of Gastric Juice*

Condition	Cases Examined	Total No. of Cells per Cu. Mm.		Epithelial Cells, per Cent		Leukocytes, per Cent	
		Average	Average Range	Average	Average Range	Average	Average Range
Normal.....	11	232	80- 530	84	70-89	16	11-21
Duodenal ulcer without stenosis	6	302	145- 575	77	63-86	23	14-32
Stenosis.....	5	1,040	510-2,370	67	63-71	33	29-37
Gastric ulcer.....	3	425	205- 740	68	53-80	32	20-47
Gastric carcinoma.....	5	2,455	810-5,055	64	57-63	36	32-43
Postoperative states.....	7	1,091	295-2,565	71	61-86	29	14-39
Gastritis.....	13	1,812	290-6,800	60	31-81	40	19-60

*Gastric Ulcer.*—Unfortunately, only 3 cases of benign gastric ulcer were encountered during the time this study was made. All 3 patients were examined gastroscopically. One patient, whose gastric ulcer was surrounded by only a slight area of gastritis, had a normal average total cell count of 330 cells per cubic millimeter, with 20 per cent leukocytes. The other 2 had elevated leukocyte averages. Although there were not enough cases for one to draw definite conclusions, the data tend to indicate that benign gastric ulcer per se does not increase the total cell count or the percentage of leukocytes in the gastric contents. Any increase of cells or leukocytes would indicate associated gastritis.

*Gastric Carcinoma.*—Five patients with gastric carcinoma had an average total cell count of 2,455 per cubic millimeter, with a range of 810 to 5,055 cells. The leukocyte average was 36 per cent, with a range of 32 to 43 per cent. Westphal,<sup>21</sup> Westermann, Vogels and Moutier<sup>22</sup> expressed agreement that the gastric contents in cases of gastric carcinoma show higher total cell counts than were noted in any

21. Westphal, K.: Ueber die Ergebnisse der Magenzellsonden, Verhandl. d. deutsch. Gesellsch. f. inn. Med. 47:390-393, 1935.

22. Moutier, F.: Cyto-diagnostic du suc gastrique et gastroscopie, Arch. d. mal. de l'app. digestif. 24:1099-1102 (Oct. 8) 1934.



of the other types of cases. This was undoubtedly due to the necrotic surface area of the tumor. The size and location of the gastric carcinoma determined in part the total cell count and leukocyte average. One patient, with a small, nonobstructing carcinoma near the pylorus, had an only slightly elevated total cell count of 810 per cubic millimeter. The associated gastritis was another important factor influencing the cytologic characteristics, since it may be slight or extensive even with small carcinomas. Mosto and Polak,<sup>23</sup> Ackerman and Gompertz<sup>24</sup> and Jekel<sup>25</sup> are among those who have mentioned that gastric carcinoma may be diagnosed by finding pieces of the carcinoma in the gastric contents. In this study no definite pieces of carcinoma were seen, although one typical mitotic carcinoma cell in the prometaphase stage of cell division was noted. In this group in particular the bacterial flora was uniformly rich.

*Postoperative States.*—Westermann<sup>16a</sup> estimated that about 15 per cent of patients who undergo gastric operations are not relieved of their symptoms in spite of unobjectionable operative procedures. As is indicated in table 2, 7 such patients were studied. The average total cell count was 1,091 per cubic millimeter, with a range of 295 to 2,565 cells. The leukocytes averaged 29 per cent, with a range of 14 to 39 per cent. Two patients with gastrojejunal ulcer were in this group. One of these, with a gastrojejunal ulcer and a patent stoma, had an average total cell count of 575 per cubic millimeter, with 19 per cent leukocytes. These values, of course, fell within the normal range. The other patient with gastrojejunal ulcer had a partially stenosed stoma and an average total cell count of 2,145 per cubic millimeter, with 34 per cent leukocytes. This again would indicate that stasis of the gastric contents is a factor in the production of gastritis. On the other hand, Schindler, Necheles and Gold<sup>26</sup> have recently pointed out that "surgical gastritis" may occur as a direct result of operative procedures, because of interference with the blood supply of the stomach. This group of 7 cases was not large enough to warrant any discussion as to the relative merit of the various types of surgical procedures.

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23. Mosto, D., and Polak, M.: Valor del examen histopatológico del jugo gástrico incluido en parafina, en el diagnóstico del cancer de estómago, *Día méd.* **10**:295 (April 18) 1938.

24. Ackerman, W., and Gompertz, L. M.: Microscopical Examination of the Fasting Stomach Contents and Its Diagnostic Value, *M. Rec.* **67**:527-532 (April 8) 1905.

25. Jekel, L. G.: Diagnosis of Carcinoma of the Stomach from a Fragment of the Tumor Obtained During Routine Gastric Analysis, *J. Lab. & Clin. Med.* **21**: 836-838 (May) 1936.

26. Schindler, R.; Necheles, H., and Gold, R. L.: Surgical Gastritis: A Study on the Genesis of Gastritis Found in Resected Stomachs with Particular Reference to the So-Called "Antral Gastritis" Associated with Ulcer, *Surg., Gynec. & Obst.* **69**:281-286 (Sept.) 1939.

*Gastritis.*—Thirteen cases of gastritis were studied. In 11 the diagnosis was verified by gastroscopic examination. No cases of atrophic gastritis were included in this study, since it represented the end stage of the inflammatory process and was analogous to the myocardial fibrosis seen with coronary arteriosclerosis. One patient was included in this group who did not have gastric symptoms at the time of examination but who had an average total cell count of 1,205 per cubic millimeter, with 34 per cent leukocytes. This patient, however, had quiescent pulmonary tuberculosis with some bronchiectasis. This case probably represented mild secondary gastritis as described by Kauffmann<sup>26</sup> and by Konjetzny<sup>28</sup> which had not reached a stage of severity in which it would cause gastric symptoms. In such a patient gastric symptoms would probably develop if an infection should develop anywhere in the body. This is analogous in principle with the "latent chronic" phase of chronic glomerulitis as described by Bell.<sup>27</sup> The average total cell count of the group with gastritis was 1,812 per cubic millimeter, with a range of 290 to 6,800 cells. The leukocytes averaged 40 per cent, with a range of 19 to 69 per cent. The highest single reading of a total count of 10,840 cells per cubic millimeter, with 87 per cent leukocytes, was found in a case of gastritis.

#### COMMENT

This study of 50 cases should be regarded as a preliminary report. A study of the cellular elements of the gastric contents, in our judgment, offers great possibilities for supplementing the information obtained by chemical, roentgen and gastroscopic procedures. This method of study is relatively simple and inexpensive. It also enables one to make numerical estimations indicating the severity of the gastritis present and the efficacy of treatment. The fact that our results are more or less in accord with those of other well known investigators lends authority to the procedure. Moreover, our conclusions from the standpoint of purely cytologic examination are in agreement with previous gastroscopic and surgical ones as regards gastritis in its secondary manifestations. For example, our observations confirm those of Walters and Sebening<sup>28</sup> with respect to the incidence of gastritis in the United States, especially in association with ulcer. They are also in accord with Schindler's<sup>29</sup>

27. Bell, E. T.: Diseases of the Urinary System, in *A Text-Book of Pathology*, ed. 2, Philadelphia, Lea & Febiger, 1934, pp. 382-402.

28. Walters, W., and Sebening, W.: A Comparison of Lesions Associated with Duodenal Ulcer in Germany and in the United States, *Minnesota Med.* **15**:579-584 (Sept.) 1932.

29. Schindler, R.: *Gastroscoy: The Endoscopic Study of Gastric Pathology*, Chicago, University of Chicago Press, 1937, pp. 270-275.

observations that gastritis does not appear in stomachs with well adapted and rhythmically contracting stomas.

#### SUMMARY

A practical technic for study of the cellular elements of the gastric contents after an alcohol test meal is described in detail. Neutralizing the gastric acids *in vivo* was a definite aid in preserving the integrity of the cytoplasm of the cells of the gastric contents, but the nuclei could usually be differentiated from one another even though their cytoplasm had been digested away.

Squamous cells constituted 16 per cent of the cells observed in smears of gastric contents, but they should be ignored when this method of study is used for the diagnosis of gastritis. The epithelial cells were the result of desquamation, while the leukocytes represented true cellular exudation. The leukocytic migration, or leukopedesis, probably occurs from capillaries near the gastric crypts into the lumens of the crypts and then into the lumen of the stomach. A rough estimation of the amount of mucus in the gastric contents showed that this was not in direct proportion to the degree of gastritis present. The only uniform trend of bacterial flora was in the group of cases of gastric carcinoma in which it was greatly increased.

Patients with uncomplicated duodenal ulcer presented an essentially similar picture to that noted in a normal group. Patients with duodenal ulcer and stenosis had elevated total cell counts and leukocyte averages, indicating secondary gastritis. The results of the test in 3 cases of benign gastric ulcer would indicate that with gastric ulcer, *per se*, the gastric contents have essentially normal cytologic characteristics. Any elevated cell counts or leukocyte averages indicate associated gastritis. In cases of gastric carcinoma there are usually markedly elevated total cell counts and moderately elevated leukocyte averages. The size, type and location of the carcinoma as well as the associated gastritis are factors influencing the cytologic structure of the gastric contents. Seven patients with persistent gastric symptoms after gastric operations had slightly elevated total cell counts and leukocyte averages. Patients with gastrojejunal ulcer and a well functioning stoma had an essentially normal cell picture. If the stoma was partially stenosed, however, the total cell count and leukocyte average became elevated. Thirteen patients with gastritis presented elevated total cell counts and leukocyte averages. Multiple readings from fractionally aspirated specimens of gastric juice should be averaged in preference to relying on single specimens. This method of study offers great possibilities for the diagnosis of gastritis and permits a numerical evaluation of the response of the gastric mucosa to therapeutic measures.

# GENERAL ABDOMINAL LYMPHADENOPATHY

WITH SPECIAL REFERENCE TO NONSPECIFIC MESENTERIC ADENITIS

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It has come to be fairly recognized that there exists in children and young adolescents an acute abdominal condition of moderate or severe grade, similar in its general manifestations to appendicitis, diverticulitis, etc., but in which the predominant discoverable observations at operation consist only of an inflammatory enlargement of the mesenteric and retroperitoneal lymph glands in the ileocecal angle. The condition appears to be more common than is thought (Struthers;<sup>1</sup> Freeman;<sup>2</sup> Heusser;<sup>3</sup> Wilensky and others<sup>4</sup>), and in a series collected by Short<sup>5</sup> it was found to occur in 6 per cent of 200 cases. The condition comes mostly under the direct observation of pediatricians and surgeons. An atmosphere of anxiety prevails.

The general clinical facts concerning this condition are as follows:

The patient is usually between 3 and 18 years of age (Wilensky;<sup>4a</sup> Short;<sup>5</sup> Freeman;<sup>2</sup> Struthers<sup>1</sup>), but the condition has been reported as occurring in young adults, and in 200 cases collected by Heusser,<sup>3</sup> Guleke<sup>6</sup> and Sennels<sup>7</sup> the incidence was chiefly in the age groups between 10 and 20 years. The illness assumes for the most part the picture of a fairly acute attack, but recurrences and recrudescences of

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1. Struthers, J. W.: Mesenteric Lymphadenitis Simulating Appendicitis, *Edinburgh M. J.* **27**:22 (July) 1921.

2. Freeman, L.: Surgical Significance of Mesenteric Lymphadenitis, *Surg., Gynec. & Obst.* **37**:149 (Aug.) 1923.

3. Heusser, H.: Die Schwellung der mesenterialen Lymphdrüsen, *Beitr. z. klin. Chir.* **130**:85, 1923.

4. (a) Wilensky, A. O.: Mesenteric Lymphadenitis, *M. Rec.* **98**:770 (Nov. 6) 1920; Nonspecific Granuloma of the Intestine, *M. J. & Rec.* **135**:445 (May 4) 1932. (b) Wilensky, A. O., and Hahn, L. J.: Mesenteric Lymphadenitis, *Ann. Surg.* **83**:812 (June) 1926. (c) Wilensky, A. O., and Moschcowitz, E.: Nonspecific Granuloma of the Small Intestine, *Am. J. M. Sc.* **173**:374 (March) 1927.

5. Short, A. R.: Symptoms Due to Mesenteric Lymphadenitis, *Lancet* **2**: 909 (Nov. 3) 1928.

6. Guleke, E.: Die Hyperplasie der Mesenterial-Lymphdrüsen, *Arch. f. klin. Chir.* **133**:517, 1924.

7. Sennels, A.: Hyperplasia of Mesenteric Glands (Mesenteric Adenitis), *Ugesk. f. læger* **87**:1125 (Dec. 17) 1925.

the condition may uncommonly occur and lead to the clinical picture of a chronic ailment.

The symptoms of an acute attack are as follows: The patient is seized with abdominal pain, which is of varying severity and can generally be traced to the right side of the lower part of the abdomen, occasionally extending to the left side. The abdominal symptoms are not as distinct as those of appendicitis or of some other acute intra-abdominal conditions. In the absence of complications there is no boardlike hardness of the abdominal muscles, no Blumberg pain, no Rovsing symptom, no resistance and no vomiting; there remains only the pain to deep palpation, centering about the navel or in the right iliac fossa. In the cases of more serious involvement there is evidence of a definite general toxic reaction as shown by a high temperature and a high leukocyte count (20,000 per cubic millimeter) in contrast to the relatively insignificant local symptoms.

The inflamed mesenteric glands present all kinds of nonspecific inflammation, from the simple hyperplasias and sinistral catarrhal exudates to purulent fusions and frank abscess formation. Nonspecific giant cell formations sometimes occur. In cases of severe involvement forms of peritonitis occur, either by transudation of infectious material or by perforation of glandular abscesses.

In spite of the fact that the mesenteric lymphadenitis is always secondary, it presents itself with its clinical symptoms as a complete, independent picture in which sometimes the source of infection is veiled and/or at other times difficult or impossible to locate. The name "lymphadenitis mesenterialis" has the same justification as "lymphadenitis colli" when after the reduction and retrogression of an intraoral infection the inflammation of the cervical lymphatic apparatus becomes dominantly prominent. Mesenteric lymphadenitis is thus frequently the first concrete revelation of an intra-abdominal inflammation in a form simulating a mild or symptomless appendicitis, typhlitis or enteritis.

This form of mesenteric adenitis must be differentiated from and/or integrated with the acute intra-abdominal conditions common to this period of life, such as appendicitis, diverticulitis of Meckel's diverticulum or intussusception, and possibly from influenza and other forms of infectious gastrointestinal disease. As the clinical picture and the available laboratory diagnostic aids are not specific, the differentiation is always difficult and frequently impossible. One is impelled by anxiety to make a correct differentiation, and commonly one is compelled to establish the true condition of affairs only by means of an operative abdominal exploration.

The attacks subside as a rule. In some cases there is only one attack; in others (uncommonly) the attacks recur at intervals of weeks or

months, the child being apparently well during the intervening periods. In some the attacks will continue to recur until, under the diagnosis of chronic appendicitis, an appendectomy is done, and in a large proportion of these there will be freedom from symptoms thereafter. In the remainder recurrences still follow at later periods in the continued absence of any definite knowledge as to the cause of the abdominal pain and/or even when the apparent or discoverable source of infection is healed. For example, it is possible that pain will remain after the removal of an appendix which shows pathologic evidence of disease.

Such intra-abdominal lymphadenopathy, in contradistinction to lymphadenopathy in other parts of the body, has never received proper attention. The purpose of this communication is to study this subject with special reference to that form of intra-abdominal lymphadenopathy which since my first communication in 1920 has been, for want of a better terminology, classified among the "nonspecific" diseases.

The term "nonspecific" as used in this communication is intended to convey the thought that the essential cause of the glandular enlargement under discussion is not specifically known at the time of writing. The term might be better paraphrased as "nonclassifiable." In conformity with this, there will be no reference to specific forms of lymphadenopathy—either those due to specific infecting agents, such as those causing typhoid, tuberculosis or syphilis; those due to neoplastic change, such as the forms of lymphosarcoma; or those bordering on inflammatory or neoplastic disease, such as Hodgkin's disease—except as an incidental matter unavoidably suggested by the discussion of nonspecific mesenteric adenitis.

This résumé of my experiences with nonspecific adenopathy in the mesenteric lymph nodes and of other published experience has been stimulated by the considerable and progressive interest shown by the increasingly large number of reports in the literature. Because mesenteric adenitis is fairly common; because it may simulate any of numerous acute surgical conditions; because in many cases the lesion seems limited to the lymph nodes and no primary, preceding lesion is demonstrable, and because, in other cases, incompletely understood pathologic change is present in anatomically related tissues or structures, a diversity of opinion has resulted in the explanation of the pathogenesis and biologic development of nonspecific lymphadenopathy in the mesenteric lymph nodes, in the interpretation of the demonstrable pathologic anatomic manifestations and in the differentiation and integration of the lymph node lesion in the total clinical entity.

Because of these facts and in an attempt to find the true biologic and etiologic place of mesenteric adenitis, I shall assemble, correlate and evaluate all the available factual matter and experience regarding nonspecific mesenteric lymphadenitis and compare this with that relating

to other forms of known mesenteric lymphadenopathy. The proper integration of this factual matter should enable one to establish the accuracy of any conclusion the assumption of which seems to be indicated.

#### HISTORICAL CONSIDERATIONS<sup>8</sup>

Mead<sup>9</sup> has recently summarized the available historical knowledge. It appears that the vague references found in the writings of Herophilus were crystallized into definite knowledge by the Italian Aselli<sup>10</sup> in 1627. In 1651 a Frenchman, Pecquet,<sup>11</sup> was able to trace the flow of the lymph through the thoracic duct and the subclavian vein into the heart. In 1653, Rudbeck<sup>12</sup> (Sweden) discovered the lymph vessels of the mesentery, and in 1664, Swammerdam<sup>13</sup> (Netherlands) demonstrated the valves in the lymphatic vessels. In 1677, Peyer<sup>14</sup> (Switzerland) described the lymphoid follicles in the terminal part of the ileum, since known by his name (Peyer's patches). Between 1765 and 1770, Hewson<sup>15</sup> (England) compared similar lymphatic structures in birds, fishes and reptiles with those previously described as observed in human beings.

In the eighteenth century, Hunter and Hunter<sup>16</sup> recognized and emphasized the limitation of the absorptive function of these vessels. In 1825, Gaspard<sup>17</sup> showed that part of the absorptive function also occurred through the venous radicles. In 1850 Ludwig<sup>18</sup> demonstrated the modern view of the physiologic relation between the capillary blood vessels and the lymphatic channels through the diffusion of fluid from the blood channels and the formation of lymph. In 1861 and 1863, Hiss<sup>19</sup> investigated the structure of the lymphatic glands and the lymphatic vessels.

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8. Garrison, F. H.: *History of Medicine*, Philadelphia, W. B. Saunders Company, 1921.

9. Mead, C. H.: *Mesenteric Lymphadenitis Simulating Acute Appendicitis: A Quantitative Study of Size of Normal Mesenteric Lymph Nodes*, *Arch. Surg.* **30**:492 (March) 1935.

10. Aselli, G.: *De lactibus sur lacteis venis*, Milan, apud J. B. Bedellum, 1627.

11. Pecquet, J.: *Experimenta nova anatomica*, Paris, J. Tollium, 1651.

12. Rudbeck, O.: *Nova exercitatio anatomica exhibens ductos hepaticos aquosos et vasa glandularum serosa*, Westerås, Sweden, 1653.

13. Swammerdam, cited by Garrison.<sup>8</sup>

14. Peyer, J. C.: *Exercitatio anatomico-medica de glandulis intestinorum*, Schaffhausen, Onuphrius et Waldkirch, 1677.

15. Hewson, W., cited by Garrison.<sup>8</sup>

16. Hunter, J., and Hunter, W., cited by Garrison.<sup>8</sup>

17. Gaspard, B.: *Mémoire sur l'introduction des substances dans les artères des animaux vivans*, in *J. de physiol. expér.* **5**:399, 1825.

18. Ludwig, C., cited by Garrison.<sup>8</sup>

19. Hiss, W., cited by Garrison.<sup>8</sup>

As early as 1723, Sydenham,<sup>20</sup> according to Bertein and Worms,<sup>21</sup> described enlargement of the mesenteric glands in children and Monro<sup>22</sup> (1760) described enlargement of the lymph nodes of the head, axilla and inguinal regions. More detailed pathologic knowledge of the mesenteric glands was contributed by Werner and Feller<sup>23</sup> in 1784 (atrophy and hardening of the mesenteric nodes) and by Cruikshank<sup>24</sup> in 1786 (numerical distribution of the mesenteric glands). In 1775 the term "tabes mesenterica" was coined by Ball<sup>25</sup> for this condition and has continued to be used. In 1787 Mascagni<sup>26</sup> described a form of disease which caused the lymph nodes to harden and grow smaller. Various enlargements of the mesenteric glands were further described by Virchow<sup>27</sup> in 1853.

Early reports were made from observations recorded post mortem, and knowledge regarding the lymph nodes especially came about mostly through the pathologic manifestations; enlarged mesenteric lymph nodes were found, discrete or matted together in smaller or larger masses, and there were various degrees of suppuration, caseation and/or calcification. Competent laboratory data were, of course, lacking; nevertheless, the lesion was accepted as tuberculous. As late as 1909, "tuberculous" mesenteric lymphadenitis was so little described that Mächtle<sup>28</sup> could find only 14 cases recorded in the literature. Other forms of nonspecific inflammatory lymphadenitis had not yet been differentiated and investigated.

As soon as modern abdominal surgery became established, observations of the presence of enlarged mesenteric lymph nodes increased in number. All kinds of enlargements were recorded, and because of insufficient laboratory investigation the conditions were still all assumed to be of tuberculous origin. Later there was confusion in the laboratory investigations and in their interpretation; it was not always possible to

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20. Sydenham, cited by Bertein and Worms.<sup>21</sup>

21. Bertein, P., and Worms, G.: *Les adénopathies du mésentère*, *Gaz. d. hôp.* **82**:1291, 1909.

22. Monro, A. (Secundus): *De venis lymphaticis valvulosis et de earum in primis origine*, Thesis, Leipzig, 1760; Berlin, G. A. Lang, 1761.

23. Werner, P. C. F., and Feller, C. G.: *Vasorum lacteorum atque lymphaticorum anatomico-physiologica descriptio*, Leipzig, S. L. Crusium, 1784.

24. Cruikshank, M.: *Anatomie des vaisseaux absorbants du corps humain*, translated from the English by Petite-Radel, Paris, Froullé, 1787.

25. Ball, G.: *De tabes mesenterica*, Edinburgh, Balfour & Smellie, 1773.

26. Mascagni, P.: *Vasorum lymphaticorum corporis historia et iconographia*, Sennis, ex. typog. P. Carli, 1787.

27. Virchow, R.: *Zur pathologischen Physiologie des Bluts. Die Bedeutung der Milz- und Lymphdrüsen-Krankheiten für die Blutmeschung (Leukämie)*, *Virchows Arch. f. path. Anat.* **5**:43, 1853.

28. Mächtle, H.: *Ueber die primäre Tuberkulose der mesenterialen Lymphdrüsen*, *Beitr. z. klin. Chir.* **59**:50, 1908.



demonstrate tubercle bacilli, and the differentiating interpretation of foreign body giant cells as distinguished from the Langhans cell was not often made. Finally the various cutaneous tests for tuberculosis segregated a group of conditions in which tuberculous infection could be excluded and in which cultivations of the common pyogenic organisms could be and were made from the lymph node tissue.

The modern history of mesenteric adenitis began with my communication in 1920, in which I described 3 cases illustrating different types or stages of nonspecific mesenteric lymphadenitis and pointed out that some intra-abdominal abscesses formerly ascribed to the appendix may in reality have resulted from the breaking down of the mesenteric nodes, particularly when a fecal discharge had never been noted in the course of subsequent healing of the operative wound.

Struthers'<sup>1</sup> paper in 1921 was confined to tuberculous mesenteric adenitis but is of importance for this discussion, in that Struthers pointed out, apparently for the first time, that in cases of acute or subacute appendicitis there is practically never any associated enlargement of the regional lymph nodes—a curious clinical fact easily explainable on anatomic grounds.

In 1922, Walker<sup>29</sup> emphasized the importance of keeping in mind the possibility of calcification in the mesenteric nodes, which roentgenographically has repeatedly been misinterpreted as ureteral calculi. This phase of the subject will be discussed later.

In 1923, Heusser<sup>3</sup> brought out the fact that there was no definite basis for considering some of these conditions tuberculous. He examined the excised inflamed glands bacteriologically and pathologically and failed to obtain evidence of tuberculosis by culture, guinea pig inoculation or the antiformin method. Neither could he demonstrate bacteriologically the presence of any other organism. He gave a résumé of the clinical findings based on 40 cases, in 29 of which the patients were under 15 years of age. Heusser speculated concerning the possible role of intestinal parasites in the etiology of the syndrome.

In 1924, Symmers<sup>30</sup> pointed out that Hodgkin's disease produces a type of mesenteric lymphadenitis which can be confused with the simple or with the tuberculous variety.

In 1925, Wagner<sup>31</sup> reported a case in which the lymphadenitis had a definite traumatic origin, a blow over the cecum producing typhlitis with subsequent local adenitis.

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29. Walker, J. T.: Relation of Calcified Abdominal Glands to Urinary Surgery. *Lancet* **2**:1213 (Dec. 9) 1922.

30. Symmers, D.: Clinical Significance of Pathological Changes in Hodgkin's Disease, *Am. J. M. Sc.* **167**:313 (March) 1924.

31. Wagner, J.: Acute Mesenteric Lymphadenitis Following Trauma and Simulating Acute Appendicitis, *Internat. J. Med. & Surg.* **38**:113, 1925.

Since 1925 increasingly frequent reports in the literature have testified to the abundant interest in this subject, especially because of its clinical importance in differentiating the lesion from other and perhaps more important surgical emergencies (appendicitis, diverticulitis, typhlitis, ileitis, etc.). Most of the literature has come from the United States and France; a little has come from Italy, and very little indeed has come from Germany. This probably indicates and reflects changed world conditions in scientific and medical matters. The observers, mostly clinicians, include, to mention only a few, Brennemann,<sup>32</sup> (relation of throat infection to abdominal infection), Mead<sup>9</sup> (anatomic and clinical studies), Ireland<sup>33</sup> (studies in etiology), Adams and Olney,<sup>34</sup> Klein<sup>35</sup> and Foster<sup>36</sup> (all clinical studies), Alvarez,<sup>37</sup> Parini<sup>38</sup> and Golden<sup>39</sup> (chronic abdominal pain in relation to enlargement of the abdominal lymph glands and to calcified mesenteric glands). The substance of the observations of these authors will be referred to many times in the following communication.

#### ANATOMY<sup>40</sup>

Accurate knowledge of the normal anatomy and distribution of the lymph glands is necessary and for this subject should include especially the nodes correlated usually with the small intestine and the proximal half of the large intestine.

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32. Brennemann, J.: The Abdominal Pain of Throat Infections, *Am. J. Dis. Child.* **22**:493 (Nov.) 1921; The Clinical Significance of Abdominal Pain in Children, *Surg., Gynec. & Obst.* **34**:344 (March) 1922; Throat Infections in Children, *Arch. Pediat.* **42**:145 (March) 1925; The Abdominal Pain of Throat Infections in Children and Appendicitis, *J. A. M. A.* **89**:2183 (Dec. 24) 1927.

33. Ireland, J.: Etiologic Factors of Mesenteric Lymphadenitis, *Arch. Surg.* **36**:292 (Feb.) 1938.

34. Adams, W. E., and Olney, M. B.: Mesenteric Lymphadenitis and the Acute Abdomen: Report of Thirteen Cases, *Ann. Surg.* **107**:359 (March) 1938.

35. Klein, W.: Nonspecific Mesenteric Adenitis: A Report of One Hundred and Forty Cases, *Arch. Surg.* **36**:571 (April) 1938.

36. Foster, A. K., Jr.: Disease of the Mesenteric Lymph Nodes: Its Relation to Appendicitis, Infections of the Gastro-Intestinal Tract and Generalized Diseases; Report of One Hundred and Twenty-Three Cases; Discussion of Possible Etiology and Treatment, *Arch. Surg.* **36**:28 (Jan.) 1938.

37. Alvarez, W. C.: Mesenteric Lymphadenitis in Adults: A Cause of Pseudo-Appendicitis, Indigestion, Diarrhea and Arthritis, *M. Clin. North America* **14**:605 (Nov.) 1930.

38. Parini, A.: Contributo allo studio delle sindromi addominali da adenopatie del mesentere, *Arch. ital. di chir.* **56**:314, 1939.

39. Golden, R.: Observations on Small Intestinal Physiology in the Presence of Calcified Mesenteric Lymph Nodes, *Am. J. Roentgenol.* **35**:316 (March) 1936.

40. Ludwig, C. F. W., and Schweigger-Seidel, F.: Die Lymphgefäße der Fascien und Sehnen, Leipzig, S. Hirzel, 1872. von Bergmann, in Holmes, T.: A System of Surgery, Theoretical and Practical, in Treatises by Various Authors, revised by J. H. Packard, Philadelphia, H. C. Lea's Son & Co., 1881.

In 1786, Cruikshank<sup>24</sup> thought that the mesenteric nodes varied in number from one hundred and thirty to one hundred and fifty. In 1787, Mascagni<sup>26</sup> had a more detailed knowledge of the lymph nodes in general—their general shape, their organization into groups and the relation of their growth to that of the body in general and to the age of the patient (pubescent enlargement and senescent atrophy). A century later, in 1889, Wullenweber<sup>41</sup> undertook the first quantitative study of the size of the abdominal lymph nodes. The last reported study along these lines was done by Mead<sup>9</sup> in 1935. He thought that the total number of mesenteric nodes varies greatly (from about thirty in a premature stillborn infant to nearly three hundred in another full term stillborn infant), and he expressed the opinion that there is evidence of an increase in the size of the normal glands up to puberty.

The modern knowledge of the normal anatomy of the mesenteric lymph nodes<sup>42</sup> is contained in all modern textbooks, and an especially fine description is given in Tobias' translation of Rouvière's<sup>42a</sup> book on the anatomy of the human lymphatic system. All of these sources have been used for the following résumé.

*The Lymph Nodes of the Mesentery.*—These nodes, the mesenteric nodes proper, form a group which is numerically the greatest in the body. Cruikshank<sup>24</sup> appraised their number as approximately one hundred and thirty to one hundred and fifty; Krause,<sup>43</sup> as one hundred to two hundred, and Descompes and Turnesco,<sup>44</sup> as forty-five to one hundred and eighty. The number of lymph nodes found in the mesentery between its intestinal and fixed borders is greater opposite the jejunum than opposite the ileum and decreases as the ileocecal junction is approached. The number of lymph nodes in any given segment of the mesentery is directly proportional to the width between its fixed and free borders (Descompes and Turnesco;<sup>44</sup> Turnesco<sup>45</sup>). As a general rule the largest nodes are those at the root, and the nodes gradually become smaller as the intestine is reached. The mesenteric lymph nodes

41. Wullenweber, E.: *Zur normalen und pathologischen Anatomie der Mesenterialdrüsen*, Kiel, A. F. Jensen, 1889.

42. (a) Rouvière, H.: *Anatomy of the Human Lymphatic System*, translated by M. J. Tobias, Ann Arbor, Mich., Edwards Brothers, Inc., 1938. (b) Rouvière, H., and Valette, G.: *De la régénération des ganglions lymphatiques et du rétablissement de la circulation interrompue dans une voie lymphatique*, Ann. d'anat. path. **14**:79 (Feb.) 1937.

43. Krause, C. F. T.: *Handbuch der menschlichen Anatomie*, ed. 3, Hanover, Hahn, 1876-1881.

44. Descompes, P., and Turnesco, D.: *Les vaisseaux lymphatiques du gros intestin et leurs ganglions*, Bull. et mém. Soc. de chir. de Paris **48**:1345 (Dec. 6) 1922.

45. Turnesco, D.: *Le mésentère. Etude d'anatomie chirurgicale*, Thesis, Paris, no. 339, 1923.

appear to be distributed without order in the substance of the mesentery. One may, however, divide these nodes into three principal groups: (*a*) the peripheral, or juxtaintestinal, (*b*) the middle and (*c*) the central.

The mesenteric glands are situated between the layers of the mesentery and are grouped as follows: one group adjacent to and in correlation with the small intestine, in the terminal arborization of the superior mesenteric artery; a second among the primary branches of the vessels, and a third along the trunk of the artery.

*The Cecal and Appendical Lymph Nodes.*—These accompany the branches of the ileocolic artery. Each of these branches is accompanied by a group of lymph nodes, all of which represent offshoots of a central chain which is arranged along the main stem of the ileocolic artery.

*The Ileocolic Glands.*—These glands number from ten to twenty, surround the ileocolic artery and are for the most part grouped near the duodenum and on the lower part of the trunk and branches of the artery, as follows: (*a*) ileal, in relation to the ileal branch of the artery; (*b*) anterior ileocolic, near the wall of the cecum; (*c*) posterior ileocolic, in the angle between the ileum and the colon but behind the cecum at its junction with the ascending colon; (*d*) a single gland, between the layers of the mesenterium of the vermiform process, and (*e*) right colic, along the medial side of the ascending colon.

The mesenteric glands receive afferents from the jejunum, the ileum, the cecum, the vermiform process and the ascending and transverse parts of the colon; their efferents pass to the preaortic glands.

*The Appendical Group.*—This is inconstant. It was reported by Lafforgue<sup>46</sup> to be present in only 27 per cent of the cases and by Tixier and Viannay<sup>47</sup> to be present in 54 per cent. When this group is present, there is usually found but one node, placed either at the medial angle of the base of the appendix, in the mesoappendix or more laterally, "in the angle which separates the ileocaecal appendix and caecum from the small intestine . . . between the two leaflets of the appendicular fold" (Clado<sup>48</sup>). This last location is the usual one for the "appendicular lymph node," according to Clado.<sup>48</sup> In addition, disseminated nodules may be found in the mesoappendix, since the number of appendical nodes may reach four (Lafforgue<sup>46</sup>) or even eight (Tixier and Viannay<sup>47</sup>). And, finally, the appendical group may be represented by an ileocolic

46. Lafforgue, E.: Recherches anatomiques sur l'appendice vermiculaire du caecum, J. internat. d'anat. et de physiol. **10**:141-167, 1893.

47. Tixier, L., and Viannay, C.: Notes sur les lymphatiques de l'appendice iléo-caecal, Lyon méd. **86**:471, 1901.

48. Clado: Appendice caecal, anatomie, embryologie, anatomie comparée: Bactériologie normale et pathologique, Compt. rend. Soc. de biol. **4** (pt. 2):133, 1892.

lymph node which has become partially engaged between the folds of the mesoappendix. The extreme variability in the disposition of the nodes in the mesoappendix renders useless any topographic classifications which have been made of these nodes.

*The Lymphatics of the Lower Part of the Ascending Colon.*—These pass by collecting vessels to the paracolic nodes, the flow being in a downward direction, along the paracolic arterial arches toward the inferior extremity of the ileocolic chain. According to Descompes and Turnesco,<sup>44</sup> those from the upper part of the ascending colon accompany the paracolic arterial arch in an ascending manner to the lymphatic chain adjoining the middle colic artery. When the right colic artery exists, part of the lymphatic drainage from the ascending colon is also carried by the lymphatics which accompany the artery to the superior nodes of the ileocolic chain. Franke,<sup>49</sup> by experiments on the newborn, showed that some of these lymphatics also enter in connection with the perirenal lymphatic paths.

*The Ascending Ileocolic Group.*—This is composed of small paracolic nodules, placed along the ascending branch of the ileocolic artery and on the medial border of the ascending colon; they present the same general arrangement as do the other paracolic lymph nodes, to be described.

*The Anterior Cecal Group.*—This is formed by one to three small nodules. These are placed in the mesentericocecal fold raised by the anterior cecal artery, as well as on the anterior wall of the cecum below and to the outer side of this fold.

*The Posterior Cecal Group.*—This accompanies the posterior cecal artery. It appears to be a continuation of the central ileocolic chain. This group consists of a short chain of lymph nodes which commences above, at the angle formed by the ileum with the ascending colon. From this point the chain extends outward and downward, at first in the cecocolic groove and then along the posterior surface of the cecum to the vicinity of the root of the appendix.

Mead<sup>9</sup> in 1935 and Foster<sup>36</sup> in 1938 described and emphasized again the importance of these anatomic studies on the basis of the fact that accurate knowledge of the pathology of the mesenteric glands must be based on accurate knowledge of their number, topographic distribution and normal appearances and especially of their normal size. It seems impossible to obtain satisfactory data, according to Mead,<sup>9</sup> because absolutely normal glands are found only in stillborn infants, and sufficiently abundant material is difficult to obtain. For this reason Mead's<sup>9</sup> study, as he himself said, has not yielded conclusive results.

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49. Franke, K.: Ueber die Lymphgefäße des Dickdarmes, Arch. f. Anat. u. Entwicklungsgesch., 1910, p. 191.

The truth seems to be that, except for a general plan, there is no constancy in the presence, number, distribution or size. Frequently, under the stress of disease, collections of lymphadenoid tissue invisible in health to the naked eye are hypertrophied and swell until they become perceptible to the palpating finger and visible to the naked eye. For all of these reasons the possible variations are numerous.

#### PHYSIOLOGY

To differentiate a true pathologic abnormality it is necessary to understand and appreciate the general effect of nutrition, accident and disease on the morphologic appearance, size, abundance and distribution of the lymphatic glands. The report of the status lymphaticus investigation committee (Young and Turnbull<sup>50</sup>) showed that the comparison of normal and abnormal values could not be correlated well with the influence of the general forms of accident and disease (accidents, burns, hemorrhage, poisoning, epilepsy, foreign bodies, drowning, pneumonia, gastroenteritis, intussusception, volvulus, intestinal obstruction) on the amount of lymphoid tissue.

Some idea of the effect of inanition, which Mead<sup>9</sup> correlated with acute and chronic forms of infection, may be gained from Boyd's<sup>51</sup> studies, which showed that the weight of the thymus gland (an important organ in the reticuloendothelial system) decreased when illness lasted more than twenty-four hours. Pediatricians in general are in complete accord with Jackson's<sup>52</sup> conclusions that lymphoid structures, such as the mesenteric nodes, undergo atrophy with inanition and that in all acute or subacute disease processes the nodes tend to be somewhat atrophic.

Enlargement of the solitary and aggregated collections of lymphadenoid tissue of the intestinal tract and of the mesenteric glands is commonly an accompaniment of marantic conditions in infants. This probably is related to the almost constant intestinal indigestion which is present and which in turn has important relations to bacterial activity in the intestinal canal.

There seems to be a definite relation between the presence of lymphadenoid tissue and bacterial disease. The presence of extraordinary aggregations of this tissue at certain points (notably at the upper end of the alimentary canal and in the terminal part of the small intestine), where bacterial activity either commences or is reenforced and

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50. Young, M., and Turnbull, H.: An Analysis of the Data Collected by the Status Lymphaticus Investigation Committee, *J. Path. & Bact.* **34**:213 (March) 1931.

51. Boyd, E.: The Weight of the Thymus Gland in Health and in Disease, *Am. J. Dis. Child.* **43**:1162 (May) 1932.

52. Jackson, cited by Brennemann.<sup>32</sup>

reactivated, indicates that these are strategic points and that the lymphadenoid tissue is an important combatant of bacterial activity.

Thompson<sup>53</sup> has shown that this is also tied up with vitamin A activity. In the rabbit the lymphoid tissue of the alimentary canal normally contains gram-positive bacteria. A diet deficient in vitamin A produced a marked increase in the number of organisms in the lymphoid tissue, so that not only were the organisms scattered abundantly throughout the deeper follicles, but they were massed in colonies as if they were multiplying locally. Especially was this the case in the lymphoid tissue of the vermiform appendix. The lymphoid follicles also began to show signs of atrophy and, in the later stages, xerophthalmia. In these cases the lymphoid follicles were represented by only a very thin layer of leukocytes. After sufficient administration of carotene in oil it was found on postmortem examination that active regeneration was present in all lymphoid structures.

Hellman and White<sup>54</sup> and Hammar<sup>55</sup> noted in cases of various general illnesses and infections that the lymph nodes apparently remain essentially unchanged and that local conditions do not affect the entire lymphoid structure. This, however, is a matter only of degree of involvement, and one should not be misled by this statement. It is important to remember that ordinarily and in any and all specific instances local infections do have secondary effects in the lymph nodes which are anatomically in relation with the seat of the primary infection and that these become swollen, reddened and the seat of an inflammatory reaction. In the discussion of mesenteric adenitis, especially, this should be kept in mind, and it will be referred to many times in this communication. Hellman and White<sup>54</sup> and Hammar<sup>55</sup> expressed the belief that the reaction of the lymphoid tissues to infection is late and that it proceeds parallel to the formation of antibodies.

This miscellaneous evidence is presented to emphasize the difficulties, more than occasionally encountered, which make difficult or of doubtful accuracy any interpretation of any lymph node enlargement which, encountered during a laparotomy, is not easily correlated with the clinical picture in any or all of its manifestations.

A constant variable physiologic fluctuation occurs with the different phases of life even during relatively healthy periods and is a nonspecific phenomenon common to many diseases. For instance, fever has an

53. Thompson, H. G.: The Lymphoid Tissue of the Alimentary Canal, *Brit. M. J.* **1**:7 (Jan. 1) 1938.

54. Hellman, T. J., and White, G.: Das Verhalten des lymphatischen Gewebes während eines Immunisierungsprozesses, *Virchows Arch. f. path. Anat.* **278**:221, 1930.

55. Hammar, J. A.: Zur Frage der Thymusfunktion, *Ztschr. f. mikr.-anat. Forsch.* **25**:97 (Aug.) 1931.

effect on the lymph nodes; it decreases the delivery of the lymph into the peripheral circulation. This has recently been studied by Doan.<sup>56</sup> The hyperpyrexia was produced in many ways, including physical and bacteriologic means. Unless the period of sustained fever is unduly prolonged, increased circulation and regeneration occur fairly quickly, and this can be measured in terms of the leukocytosis which follows.

The superlatively developed absorptive function of the intestinal tract combined with the constant presence of bacteria in the intestinal lumen creates a situation in which the passage of bacteria from the interior of the bowel into the associated lymphatic vessels and glands must be considered an almost normal and physiologic phenomenon. Although manifestations of the reaction of the host's defense mechanism against this continuous onslaught of bacteria (i. e., disease) are not apparent, it must be true that lymphatic enlargement will take place and in certain instances persist. In the ordinary stress of health and disease and under proper circumstances this would tend to complicate attempts at integration of the presence of enlarged mesenteric nodes into a given symptom complex in which other pathologic change is not demonstrable. Similar lymphatic enlargements are commonly seen in the neck or in the axilla and indicate to the trained clinician a similar mechanism and pathogenesis.

According to Rouvière and Valette<sup>42b</sup> and Teneff,<sup>57</sup> a certain amount of regeneration of the lymph glands can take place after their destruction by injury or disease.

#### ETIOLOGY

The following résumé of the available factual knowledge regarding the etiology<sup>58</sup> of general intra-abdominal and/or nonspecific mesenteric

56. Doan, C. A.: Peripheral Blood Phenomena and Differential Response of Bone Marrow and Lymph Nodes to Hyperpyrexia, *Radiology* **30**:382 (March) 1938.

57. Teneff, S.: Recherches expérimentales sur la guérison des plaies, sur la néoformation, et sur les greffes autoplastiques des ganglions lymphatiques, *Lyon chir.* **31**:540 (Sept.-Oct.) 1934.

58. Acuna, M.; Brachetto-Brian, D., and Macera, J. M.: Infection bacillaire d'origine intestinale chez un enfant de deux ans, *Compt. rend. Soc. de biol.* **93**:1014, 1925. Boettiger, K.: Zur Casuistik der Purpura fulminans, *Arch. f. Kinderh.* **85**:239 (Nov. 27) 1928. Brunsgaard, E., and Thyrotta, T. L.: Gonococcus Meningitis with Gonococcus Purpura, *Norsk mag. f. lægevidensk.* **85**:809, 1924. de las Alencas, E. L.: Tuberculosis de los ganglios mesentericos primitivos y congenita, *Arch. españ. de pediat.* **9**:687, 1925. Guelliot, O.: Note sur trois cas de purpura infectieux foudroyant, *Union méd. et scient. du nord-est* **8**:25, 1884. Hollenbach, F.: Pseudoappendizitis, hervorgerufen durch Tuberkulose der Mesenteriallymphdrüsen, *Deutsche med. Wchnschr.* **47**:125 (Feb. 3) 1921. Iselin, H.: Durchbruch der vereiterten tuberkulösen mischinfizierten Mesenterialdrüsen, *Cor.-Bl. f. schweiz. Aerzte* **48**:1569, 1918. König: Purpura fulminans bei ein 19 monatigen Kinde, *Ztschr. f. Kinderh.* **32**:282, 1922. Le Bourdellès, B.: De la méningo-coque à



adenitis falls into a number of classifications. Some of these give direct evidence, and the others are of variable value as indicating by analogy important positive and negative information regarding the etiology and pathogenesis of nonspecific mesenteric adenitis.

*Anatomic Variations.*—Royster's<sup>59</sup> assumption might possibly fall into the class of anatomic variation. He stated the opinion that the cause in some cases of mesenteric lymphadenitis is a lymphatic block around the appendix and that the removal of the appendix mechanically releases the block. Nevertheless, it seems to me that this is forcing the issue much too hard. Whether this, too, may have some relation to the suggestion of Ireland, that a kinking, twisting or obliteration of the lumen of the appendix may be a possible factor in some patients, is highly problematic and is not very well supported by an experience of only 2 cases.

*General Factors.*—A list of the agents which can cause generalized lymphadenopathy (in which the mesenteric glands may take part) includes many besides the following conditions: infections of the upper respiratory tract, glandular fever, exanthems, typhoid, influenza, tuberculosis, syphilis, many cutaneous diseases, poisoning due to certain metals, marked intestinal inflammation, ulcers of the intestines (especially those of long duration), actinomycosis, leukemia, sarcoma, Hodgkin's disease, metastatic carcinoma, rickets, scurvy, status lymphaticus, foci of infection of various types and even intestinal stasis. As far as mesenteric adenitis of the kind under discussion in this paper is concerned, the probability is that in many cases the assumed cause of mesenteric adenitis is only a conjecture, in which case the lymphadenopathy could conceivably be related to any one of the aforementioned factors.

A bizarre case of generalized adenopathy in which there was mesenteric involvement was reported by Barker and Wood,<sup>60</sup> of the Johns Hopkins Hospital. In 1919 and in 1932 attacks of "influenza" in an adult Negro were followed by a progressive development of rather severe thyrotoxicosis. In October 1932 a course of iodine (compound tincture, 3 cc. per diem) was followed by eosinophilia and persistent fever, after which the iodine was omitted temporarily to be resumed

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forme purpurique, Presse méd. **33**:660, 1925. Lund, F. B.: Tuberculosis of the Mesenteric Glands Simulating Appendicitis, Boston M. & S. J. **167**:918, 1912. McCrick, T.: Purpura Fulminans as a Sequel of Scarlet Fever, Brit. J. Child. Dis. **9**:154, 1912. Melman, R. J.: Tabes Mesenterica Following Influenza, New York M. J. **113**:147 (Jan. 22) 1921. Morawitz, P.: Zum Problem der Purpura fulminans, München. med. Wchnschr. **73**:1559 (Sept. 17) 1926. Moreau, L., and van Bogaert, L.: Tuberculose primitive des ganglions du mésentère, Arch. franco-belges de chir. **25**:888, 1922. Risel, H.: Ein Beitrag zu den Purpura-Erkrankungen, Ztschr. f. klin. Med. **58**:163, 1905.

59. Royster, cited by Freeman.<sup>2</sup>

60. Barker, W. H., and Wood, W. B.: Severe Febrile Iodism During the Treatment of Hyperthyroidism, J. A. M. A. **114**:1034 (March 23) 1940.

(saturated solution of potassium iodide) with disastrous effect as regards intensification of all the symptoms of iodism including dryness of the mouth and throat, papular rash, high fever (with no demonstrable streptococci or diphtheria bacilli in the throat and a negative blood culture) and finally death twenty-one days after the iodine therapy had been instituted.

The postmortem diagnosis was "hyperplasia of the thyroid; enlargement of the thymus; slight cardiac hypertrophy; scars in the myocardium; peculiar miliary lesions of necrosis and inflammation with eosinophils in the skin, tongue, tonsils, lungs, lymph nodes, spleen, liver, kidneys, ureters, epididymides, testes, prostate, stomach, heart and aorta; acute splenic tumor; eosinophilia (blood); acute tonsillitis; great enlargement of the lymph nodes; purulent bronchitis; hemorrhages in the lungs, and scars in the pleura." "The axillary and inguinal lymph nodes were markedly enlarged with individual nodes up to 4.5 to 2.5 cm. in diameter. The bronchial nodes were slightly enlarged, and there was questionable slight enlargement of the mesenteric and retroperitoneal nodes. In the intestine the Peyer's patches did not seem to be enlarged. The cut surface of the nodes was gray with areas of hemorrhage. Microscopically there was marked vaso-dilatation, the sinuses were filled with mononuclear cells; there was hyperplasia of the lymphoid tissue and, in some areas, fresh hemorrhage."

The portal of entry for this lymphatic infection is undoubtedly the necrotic lesions in the throat. The progression of the glandular infection from the neck to other glands in the body is indicated by the relative size of the swelling of the lymph nodes from the neck downward to the trunk.

The curious thing about these lesions is their many points of resemblance to granulomatous lesions of the intestine, in which secondary glandular swellings have also been observed. This will be discussed later.

The following factors have special reference to nonspecific mesenteric adenitis.

*Trauma.*—Trauma was considered a factor by Wagner<sup>31</sup> in 1 case which he reported. However, I was unable to find in my own experiences or in any of those published in the literature any corroborating instance of this kind.

*Allergy.*—In 1 of the cases reported by Ireland<sup>32</sup> the author was strongly of the opinion that allergy was the causative factor. The patient had attacks of abdominal pain after appendectomy similar to those before operation. Epinephrine hydrochloride given hypodermically during the paroxysms of pain gave relief. Eggs, pineapples and blueberries were removed from the diet, and the attacks ceased immediately and had not recurred eleven months after the offending foods were eliminated.

One of Wise's<sup>61</sup> patients had unusually severe allergy and a chronic infection of the throat due to *Streptococcus viridans*. The statement is made without stressing any causal relation between the allergy and the mesenteric lymphadenopathy.

61. Wise, W. D.: Mesenteric Lymphadenitis. *Ann. Surg.* 109:827 (May) 1939.

Lewis<sup>82</sup> suggested that *Bacillus melitensis*, the causative organism of undulant fever, might be an etiologic factor.<sup>83</sup> Lewis' suggestion was not accompanied, however, with substantiating proof. Nevertheless, I was able to find 1 proved case. Kennedy<sup>84</sup> reported a case in which the enlarged mesenteric glands were filled with liquid pus containing a pure culture of *melitensis* organisms.

Relation to Syphilis: In all the experience which I have had in many hospitals and in private practice, in all of which all patients have been subjected as a routine to Wassermann and Kahn tests, I do not remember ever having observed a case in which syphilitic infection could be assigned as a cause of the mesenteric enlargement. This seems to be in agreement with all other reported experience.

Infection with Filtrable Virus: Mostly on the basis of a paper by Burrows,<sup>85</sup> White<sup>86</sup> questioned the possibility that mesenteric adenitis is due to a filtrable virus. White<sup>86</sup> has found enlargement of the mesenteric glands in conjunction with a reddened appendix and a small amount of clear fluid in the right iliac fossa associated with negative results from bacteriologic study of the glands and fluid. The supposition of White<sup>86</sup> is based on Burrows'<sup>85</sup> experience with poliomyelitis, published in 1931. According to Burrows,<sup>85</sup> poliomyelitis is a disease primarily of the lymphatic system in general and not of the central nervous system, and the essential lesion is acute hyperplastic lymphadenitis. He laid special emphasis on the catarrhal and gastrointestinal symptoms which appear at the onset of the disease. He described the pathologic picture in his fatal cases as that of a general lymphoid hyperplasia, most marked in the solitary follicles of the gastrointestinal tract. Peyer's patches and the mesenteric lymph nodes.

This assumption, however, was not concurred in by Wise,<sup>61</sup> who disputed the existence of any relation between the virus infection poliomyelitis and an origin of the disease in the general lymphatic system on the ground that poliomyelitis does its damage promptly, that it confers immunity, that it does not recur and that in none of the cases in his series did any form of paralysis develop. In addition, in 1 case, in which

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82. Lewis, D., cited by Freeman.<sup>2</sup>

83. Davison, W. C.: Brucellosis, *Bull. Chicago M. Soc.* **38**:522 (March 21) 1936.

84. Kennedy, J. C.: Examination of Animals in Connection with Mediterranean Fever, in Reports of the Commission Appointed by the Admiralty, the War Office, and the Civil Government of Malta for the Investigation of Mediterranean Fever, London, Harrison & Sons, 1906, pt. 4, p. 86.

85. Burrows, M. T.: Is Poliomyelitis a Disease of the Lymphatic System? *Arch. Int. Med.* **48**:33 (July) 1931.

86. White, C. S.: Acute Mesenteric Adenitis—Filtrable-Virus Diseases, *South. Med. & Surg.* **98**:523 (Oct.) 1936. White, C. S., and Collins, J. L.: Acute Mesenteric Adenitis, *J. A. M. A.* **107**:1023 (Sept. 26) 1936.

the appendical lymph node was studied bacteriologically, no filtrable virus could be demonstrated.

Burrows<sup>85</sup> tried to correlate this experience also to experiences with abdominal influenza, but he gave no factual support for this. On the other hand, Jackson<sup>82</sup> found that, especially during epidemics, extensive forms of massive lymphadenitis were associated with influenzal infections. In the absence of better knowledge, it is not far fetched to classify the ordinary mild form of nonspecific mesenteric adenitis in the group of ill defined abdominal infections commonly called "influenza."

The suggestion that possibly mesenteric lymphadenitis might be due to the same cause as lymphogranuloma venereum<sup>87</sup> was indicated by the following factors: that frequently there is a history or evidence of a primary lesion (Thompson<sup>88</sup>); that frequently lymphogranuloma venereum is an extragenital occurrence (David and Loring<sup>89</sup>); that this disease may cause generalized lymphadenopathy (von Haam and D'Aunoy<sup>90</sup>), and, finally, that cases of lymphogranuloma venereum have been reported in which involvement of the retroperitoneal lymph nodes was observed at autopsy (Kondo;<sup>91</sup> Reichle and Connor;<sup>92</sup> Kornblith<sup>93</sup>). In 12 cases of mesenteric adenitis in which surgical exploration was done with the diagnosis of appendicitis in Ireland's<sup>93</sup> series, the Frei test yielded a negative reaction. In these, therapy with lymphogranuloma venereum antigen, as employed by Bloom,<sup>94</sup> or with solgonol (the disodium salt of 4-sulfomethylamino-2-auromercaptobenzene-1-sulfonic acid), as employed by Gohrbandt,<sup>95</sup> was not used to make a diagnosis.

**Mixed Infection:** This brings up the question of mixed infections. It is practically impossible for any specific bacterial infection to occur in the intestinal wall without the addition sooner or later of infection

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87. Cole, H. N.: Lymphogranuloma Inguinale, the Fourth Venereal Disease, J. A. M. A. **101**:1069 (Sept. 30) 1933.

88. Thompson, R. M.: Lymphopathia Venereum, J. A. M. A. **106**:1869 (May 30) 1936.

89. David, V. C., and Loring, M.: Extragenital Lesions of Lymphogranuloma Inguinale, J. A. M. A. **106**:1875 (May 30) 1936.

90. von Haam, E., and D'Aunoy, R.: Infectivity of Spinal Fluid in Lymphogranuloma Inguinale, J. A. M. A. **106**:1642 (May 19) 1936.

91. Kondo, S.: Ueber akute Peritonitis durch Lymphogranuloma inguinale verursacht, Arch. f. klin. Chir. **184**:249, 1935.

92. Reichle, H. S., and Connor, W. H.: Lymphogranuloma Inguinale, Arch. Dermat. & Syph. **32**:196 (Aug.) 1935.

93. Kornblith, B. A.: Observations on Lymphogranuloma Venereum, Surg., Gynec. & Obst. **63**:99 (July) 1936.

94. Bloom, D.: Strictures of the Rectum Due to Lymphogranuloma Inguinale, Surg., Gynec. & Obst. **58**:827 (May) 1934.

95. Gohrbandt, E.: Miterkrankung des Rectum und des Urogenitalsystems bei Lymphogranulomatosis inguinalis, Arch. f. klin. Chir. **177**:611, 1933.

by other bacterial groups (colon group, streptococcus group, etc.). Therefore, while enlargement of the mesenteric nodes may come about as a result of infection by an original group or strain of bacteria, there is good reason to believe that sooner or later added infection by other bacterial groups contribute to the original provocation and either initiate or, more probably, aggravate the lesion in the lymph nodes.

*Toxemia.*—The idea that a toxin, either of bacterial or of other origin, is the cause of enlargement of the glands in the mesentery has been much discussed.

*Nonbacterial Toxemia:* The only reference which I have been able to find in regard to any possible nonbacterial origin of any toxin absorption is in the Paris thesis of Brian,<sup>79</sup> who associated a nonspecific mesenteric adenopathy with intestinal stasis on the basis of an entire absence of demonstrable and definite anatomic, bacteriologic or other laboratory factors. I have had no experience in which this causation could possibly be assumed. Even granting the correctness of the assumption, the possibility that bacterial action is the true originating mechanism for the production and absorption of toxin is highly probable.

*Bacterial Toxemia:* Bell<sup>90</sup> expressed his own belief and that of many others, that bacterial toxins in general are the cause. Coleman<sup>75</sup> concluded that a streptococcus toxin is probably the specific causative agent. The toxin theory received especial emphasis in reference to those cases in which it is not possible to cultivate organisms from the lymph gland tissue, and, because in many of these cases bacteria can be cultivated in more or less abundance from a demonstrable lesion in the associated and related part of the alimentary canal, it seems impossible to some to avoid the conclusion that bacteria-produced toxins are the cause of the lymph node enlargement. The assumed mechanism is that of acute lymphangitis in general and commonly occurs in other parts of the body, which, because they are exposed, are susceptible to visual inspection and study. In the intestine and in the mesenteric glands such visualization is, however, not possible except at postmortem examination.

It seems impossible to me, however, to avoid the assumption that ordinarily there can be no pure toxemic cause for the lymph node enlargement. It seems better to postulate that bacteria and their developed toxins operate together to produce whatever demonstrable pathologic change there is.

#### COLLATERAL INFORMATION

*From Other Types of Specific Mesenteric Adenitis.*—Collateral information having a bearing on the etiology and especially on the bacteria-

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96. Bell, L. P.: Mesenteric Lymphadenitis Simulating an Acute Abdominal Condition, Surg., Gynec. & Obst. 45:465 (Oct.) 1927.

toxin mechanism is available from other types of mesenteric glandular enlargement in which the cause is known to be a specific organism or is assumed to be a bacterium.

(a) Typhoid Fever: An outstanding example of a form of mesenteric adenitis occurs during typhoid fever. The mechanism of progression of the demonstrable lesions is well understood to be from the intestinal ulceration into the corresponding mesenteric lymph nodes.

(b) Paratyphoid Infection: Enlargement of the mesenteric nodes occurs in about half the cases of paratyphoid infection. In 1 case, reported by Strömbeck,<sup>97</sup> the glandular enlargement was operatively demonstrated, operation having been performed under a mistaken diagnosis. The enlargement of the nodes is always rather marked (Lubarsch;<sup>98</sup> Huebschmann;<sup>99</sup> Loele;<sup>100</sup> Herxheimer;<sup>101</sup> Pick<sup>102</sup>). As far as I know, no paratyphoid organisms have been cultured from the lymph nodes in the presence of this disease.

(c) Acute Enterocolitis: Swelling of the mesenteric lymph nodes is usually present in the acute stages of acute enterocolitis and acute ileocolitis. Special mention of this has been made by Felsen<sup>76</sup> and others. The distal portion of the ileum becomes intensely reddened and swollen, and the affected parts are clearly demarcated from the adjacent uninflamed portion. The nodes along the mesenteric border of the ileum at the ileocolic junction participate in the acute process, and the mesentery becomes full of numerous reddened, succulent lymph glands.

(d) Dysentery: In the acute stages of intestinal infection by the dysentery group of organisms, there is a widespread enlargement of the lymph nodes in the mesentery; those chiefly involved are the nodes along the mesentery of the ileum, and the nodes are large and evidently inflamed. I have no knowledge of any specific bacteriologic studies of the lymph nodes in this disease, but whatever lymph node enlargement occurs is undoubtedly due to the organisms themselves and/or to the absorption of bacterial toxins along the lymph channels.

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97. Strömbeck, J. L.: Mesenteric Lymph-Adenitis: A Clinical Study, *Acta chir. Scandinav. (supp. 20)* **70**:1, 1932. Sprunt, T. P., and Evans, F. A.: Mononuclear Leukocytosis in Reaction to Acute Infections, *Bull. Johns Hopkins Hosp.* **31**:410 (Nov.) 1920.

98. Lubarsch, O.: Ueber Lymphgranulomatose, *Berl. klin. Wchnschr.* **45**: 708, 1918; Status lymphaticus, *Deutsche med. Wchnschr.* **43**:1377, 1917.

99. Huebschmann, cited by Henke and Lubarsch.<sup>72</sup>

100. Loele, cited by Henke and Lubarsch.<sup>72</sup>

101. Herxheimer, G.: Ueber die Lymphgranulomatose von ätiologischen Standpunkt, in Brauer, L.: *Beiträge zur Klinik der Infektionskrankheiten und zur Immunitätsforschung*, Würzburg, 1913, vol. 2, p. 349.

102. Pick, cited by Henke and Lubarsch.<sup>72</sup>

The intestinal lesions of bacillary dysentery may be reproduced experimentally in rabbits by the intravenous injection of either the living organisms or the toxin. The blood stream rapidly becomes sterile. From the human being positive blood cultures are rarely obtained. Felsen <sup>76</sup> repeated Flexner's theory that in the human being the intestinal lesions are essentially due to the excretion of the blood-borne dysentery toxin into the intestinal lumen; that reabsorption may occur in the early stages, and that the cycle may be repeated. Olitsky and Kligler <sup>103</sup> have described a thermostable enteric endotoxin.

The process may take place anywhere in the small or the large intestine, but there appears to be a special predilection for the distal portion of the ileum and the colon, where and wherever collections of lymphadenoid tissue occur as solitary follicles and/or are especially abundant as aggregate follicles (Peyer's patches); here the most advanced lesions are generally found.

This theory does not, however, tell the entire story. In the presence of infection with the dysentery group of organisms it is commonly possible to cultivate these organisms from the intestinal contents, and even in cases of chronic involvement this is possible, although not so frequently and with more difficulty. That under these circumstances a toxin is manufactured in the intestinal lumen is certain, and that a toxin so formed will undoubtedly be absorbed along the lymphatic apparatus into the appropriate lymph nodes is not to be disputed. To postulate an infection of the local lymph nodes by blood-borne toxin would be totally superfluous in view of the given facts and would not be in accordance with the commonly observed facts concerning the relations of any local primary lesion and the appropriate lymph node involvement in other parts of the body. Then, too, one would expect, at least rarely, the involvement of distant and not anatomically related lymph nodes by the dysentery toxin, a circumstance which I have never observed and have rarely, if ever, seen mentioned in the literature. Finally, one must not lose sight of the terrific role which mixed infection plays in dysentery, especially after the initial intensity of the bacillary infection has lessened. This has already been referred to in the section devoted to mixed infections.

(e) Nonspecific Granuloma of the Intestine: Frequent mention is made of the occurrence of enlarged, acutely inflamed, succulent glands associated with nonspecific granulomas (ileitis) of the terminal portion of the ileum (Mixer; <sup>104</sup> Koster and his associates; <sup>105</sup> Bockus and

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103. Olitsky, P. K., and Kligler, I. J.: Toxins and Antitoxins of *Bacillus Dysenteriae* Shiga, *J. Exper. Med.* **31**:19 (Jan.) 1920.

104. Mixer, C. G.: Regional Ileitis, *Ann. Surg.* **102**:674 (Oct.) 1935.

105. Koster, H.; Kasman, L. P., and Sheinfeld, W.: Regional Ileitis, *Arch. Surg.* **32**:789 (May) 1936.

Lee;<sup>106</sup> Felsen;<sup>76</sup> Stafford;<sup>107</sup> Blackburn, Hadfield and Hunt<sup>108</sup>). As was pointed out in my last review of the subject, nonspecific granulomas are apparently the end results of a multiplicity of other preceding conditions, all of which are marked by and terminate in intramural infection of the intestinal wall with abscess formation, scarring and stenoses. The pathway of infection lies along the intramural lymphatic channels, thence out along the lymph channels of the mesentery and finally into the appropriate lymph nodes. A specific cause is not known. In the absence of specific knowledge of the cause of nonspecific granuloma, it would be fatuous to speak of the bacteriologic cause of the lymph node enlargement. At the present writing the only assumption possible is that either bacteria or their toxins or both are the provocative cause of this condition also.

Peculiar anatomic pictures are commonly observed with both the intestinal lesions and the associated enlarged lymph nodes in which atypical giant cells are found. In common with that in the case of fatal iodine poisoning reported by Barker and Wood and cited previously in this communication, the pathologic picture resembles those sometimes observed in cases of nonspecific mesenteric adenopathy. This will be discussed fully in the section devoted to the pathologic features of the disease.

*From Miscellaneous Diseases.*—Collateral information is also available from other well known forms of disease in which general and/or abdominal lymphadenopathy occurs. In some of these a streptococcus seems to be the predominating demonstrable organism, and it is therefore assumed to be the etiologic agent. In others a virus is demonstrable or, because of other comparable knowledge, is believed to be present; in either case it is assumed to be the cause. In the virus diseases other infecting agents—more commonly streptococci, less commonly staphylococci—are also frequently present, and possibly these account for part of the general picture.

(a) The Exanthems:<sup>109</sup> In the various exanthems the rash commonly spreads from the external layers of the skin and appears in

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106. Bockus, H. L., and Lee, W. E.: Regional (Terminal) Ileitis, *Ann. Surg.* **102**:412 (Sept.) 1935.

107. Stafford, E. S.: Regional Ileitis and Ulcerative Colitis, *Bull. Johns Hopkins Hosp.* **62**:399 (April) 1938.

108. Blackburn, G.; Hadfield, G., and Hunt, A. H.: Regional Ileitis, *St. Barth. Hosp. Rep.* **72**:181, 1939.

109. Alvarez, W. C.; Bargen, J. A., and Brown, P. W.: Diseases of the Intestine and Some Poorly Understood Disturbances of Digestion, in Christian, H. A.: *Oxford Medicine*, New York, Oxford University Press, 1939, vol. 3, pt. 2, pp. 201-202. Swift, H. F., and McEwen, C.: Rheumatic Fever, in Christian, H. A.: *Oxford Medicine*, New York, Oxford University Press, 1939, vol. 5 pt. 1, pp. 11-38. Trask, J. D.: Scarlet Fever, in Christian, H. A.: *Oxford Medicine*, New York, Oxford University Press, 1939, vol. 5, pt. 2, pp. 519-546.



the mucous membrane of the alimentary canal (scarlet fever) or in that of the pulmonary surface (measles). Enlargement of the cervical glands occurs, more commonly by far with scarlet fever than with measles. A "red" throat is a common occurrence. In many cases the disease is ushered in with gastrointestinal symptoms; this is especially true of measles. In some cases diarrhea is present. It does not seem far fetched to ascribe these symptoms to the presence of an exanthem.

Besides the specific lesions, catarrhal processes occur in the stomach and intestines, and, in hemorrhagic patients, hemorrhages, sometimes extensive, are found, especially in the stomach, jejunum and colon. Hyperplasia of the lymphadenoid apparatus throughout the body commonly occurs but is less often present with measles. The lymph nodes swell early as a result of edema and proliferation of cells, especially in the sinuses and follicles. Cocci are often found in these lesions. The lymph follicles in the bowel and the nodes in the mesentery commonly partake of this general lymphadenopathy. In fatal cases the liver is almost always greatly enlarged and shows cloudy swelling, with necrosis in the central areas. At times there is fatty degeneration. The spleen is enlarged but soft; the pulp is soft and dark brown and in early stages contains but few leukocytes.

It seems correct to assume that the gastrointestinal symptoms are due to the lymphoid hyperplasia of the intestine and to the enlargement of its associated glands. The parallelism between the process in the neck and the process in the abdomen seems marked, and the pertinence of this to the general subject under discussion seems more than well marked.

(b) *Purpura*:<sup>110</sup> A severe and often fatal form of generalized purpura often follows some of the exanthems, especially scarlet fever and measles. It is characterized by a purpuric rash, hemorrhage, gangrene, nephritis and lymphadenopathy. The following cases are characteristic examples:

Wolff's<sup>111</sup> patient was a poorly nourished boy 2 years old. Within three hours there was a hyperacute attack of vomiting and diarrhea. Within the next twelve

110. Christian, H. A.: Visceral Disturbances in Patients with Cutaneous Lesions of the Erythema Group, *J. A. M. A.* **69**:325 (Aug. 4) 1917. Ikeda, K.: The Blood in Smallpox During a Recent Epidemic, *Arch. Int. Med.* **37**:660 (May) 1926; Purpuric Smallpox: Review of Recent Studies, *J. Lab. & Clin. Med.* **13**:440 (Feb.) 1928. Osler, W.: On the Visceral Complications of Erythema Exudativum Multiforme, *Am. J. M. Sc.* **110**:629, 1895; Visceral Lesions of Erythema Group, *Brit. J. Dermat.* **12**:227, 1900; On the Visceral Manifestations of the Erythema Group of Skin Diseases, *Am. J. M. Sc.* **127**:1, 1904; On the Surgical Importance of the Visceral Crises in the Erythema Group of Skin Diseases, *ibid.* **127**:751, 1904.

111. Wolff, A.: Ein rapid verlaufener Fall von Purpura mit tödtlichem Ausgang, *Berl. klin. Wchnschr.* **17**:254, 1880.

hours there were marked dyspnea and pain in the arms and legs. A rapid development of generalized purpura appeared within the next few hours. Death occurred fifteen hours after the onset. The postmortem examination showed swelling of Peyer's patches, of the mesenteric lymph glands and of the spleen. There were injection of the meninges and petechial hemorrhages into the gastrointestinal tract and the bladder. The left adrenal gland was enlarged.

Appenrodt's<sup>112</sup> patient was an anemic child 9 months old. Suddenly (within a few hours) there developed nosebleed, vomiting of bloody mucus and diffuse generalized purpura. There followed a confluent increase in the purpura, with marked anemia. Later there were hematuria, gangrene of an arm, hemorrhages into the tongue and melena. Examination otherwise gave negative results. Death occurred on the fourth day. The postmortem examination showed that Peyer's patches and the mesenteric lymph glands were all swollen. There were renal and subperitoneal perirenal hemorrhage, an anemic liver and no enlargement of the spleen.

Not in all of the reported cases, which were collected by Elliott,<sup>113</sup> was the abdominal involvement shown so clearly. This was true apparently in the following case, which is, however, so like the others that, because of the bacteriologic study, it is important as possibly giving a clue to the etiologic mechanism.

In Borgen's case<sup>114</sup> the manifestations began with cervical adenitis, and then marked purpura and anemia developed. Postmortem examination showed fluid blood without clotting; there was no internal hemorrhage. Culture of blood taken from the heart post mortem showed streptococci.

Undoubtedly, this severe form of disseminated purpura haemorrhagica is a phenomenon secondary to an infectious disease, and, as Borgen's case indicates, it is probably an added general infection, probably due to some strain of streptococci. As such, it indicates that the abdominal phenomena are due to metastatic manifestations within the abdomen, of which the lymphadenopathy is one. Possibly, because in some cases it is expressly stated that both Peyer's patches and the associated lymph nodes of the mesentery were involved, it might be correct to say that the added general infection finds its portal of entry through the lymphadenoid tissue of the terminal portion of the ileum. And in view of a similar mechanism in other, more clearly defined examples in this communication, it makes sense, especially in cases of abdominal lymphadenopathy. In almost all of the others cervical adenitis is present, and it is extraordinarily curious how this parallelism between the neck and the abdomen continues in these diverse forms of disease.

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112. Appenrodt: Zwei Fälle von Morbus maculosus Werlhofi im ersten Lebensjahre, *Deutsche med. Wchnschr.* 2:463, 1876.

113. Elliott, C. A.: Purpura fulminans, *Arch. Int. Med.* 3:193 (April) 1909.

114. Borgen, T.: A Case of Purpura Fulminans, *Norsk mag. f. lægevidensk.* 16:463, 1901.

(c) Infectious Mononucleosis: Of infectious mononucleosis (glandular fever) several types are described (Lehndorff and Schwarz<sup>115</sup>). In the anginose type the manifestations begin in the throat and dominate the picture. The secondary lymph node enlargement begins in the cervical region, reaches its maximum there and is followed in a few days by enlargement of the nodes in the axillary and inguinal regions; the epitrochlear glands may also enlarge. The spleen becomes palpable in about one half of the cases, but the enlargement is not as a rule great. In the glandular type (Pfeiffer<sup>116</sup>) the pharyngeal manifestations are at a minimum. An abdominal type was described by Baldridge, Rohner and Hansmann.<sup>117</sup> In a certain number of the cases gastrointestinal symptoms appear quickly and there is diffuse abdominal distress. Even though the abdominal nodes are not palpable, as a rule, in adults, it seems reasonable to assume that the abdominal symptoms are related to similar enlargements of the mesenteric and retroperitoneal nodes. Some weight is added to this assumption by the fact that in some cases the liver becomes enlarged and jaundice appears; the jaundice has been ascribed to the pressure of enlarged nodes on the hilus of the liver.

The origin of the disease in some disturbance of the intestinal tract was suggested to the earliest observers (Gourichon;<sup>118</sup> Hislop<sup>119</sup>) by the frequency of abnormal symptomatic constipation, and the path of spread therefrom throughout the body seemed to be indicated by the initial involvement of the lymph nodes in the left side of the neck. This may not be much at variance with the modern conception of a generalized infection with a preferential localization in the lymphatic apparatus (Epstein;<sup>120</sup> Du Bois<sup>121</sup>) and a secondary variable distribution in the throat, meninges, liver, etc. Further observation has shown time relations to outbreaks of influenza (Gourichon;<sup>118</sup> Josephus;<sup>122</sup>

115. Lehndorff, H., and Schwarz, E.: *Das Drüsenfieber: I. Klinik des Drüsenfiebers*, *Ergebn. d. inn. Med. u. Kinderh.* **42**:775, 1932.

116. Pfeiffer, E.: *Das Drüsenfieber*, *Jahrb. f. Kinderh.* **29**:257, 1889.

117. Baldridge, C. W.; Rohner, F. J., and Hansmann, G. H.: *Glandular Fever (Infectious Mononucleosis)*, *Arch. Int. Med.* **38**:413 (Oct.) 1926.

118. Gourichon, H.: *Essai sur la fièvre ganglionnaire*, Thesis, Paris, no. 48, 1895.

119. Hislop, J. G.: *Infectious Mononucleosis or Glandular Fever*, *M. J. Australia* **2**:557 (Nov. 7) 1925.

120. Epstein, S. H.: *Lymphocytic Meningitis*, *Correspondence*, *J. A. M. A.* **105**:1792 (Nov. 30) 1935.

121. Du Bois, A. H.: *De la pathogénie de l'angine à monocytes*, *Acta med. Scandinav.* **73**:237, 1930.

122. Josephus, J.: *The Blood Pictures of the Infectious Diseases Occurring Primarily in Childhood*, in Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1938, vol. 4, p. 2678.

Nolan<sup>123</sup>). And, according to Bernstein,<sup>124</sup> Bradshaw<sup>125</sup> attempted to correlate infectious mononucleosis with the "rheumatic group."<sup>126</sup>

All of the nodes removed at the height of the disease (usually for biopsy) are hyperplastic; lymphocytes, general reticulum, sinus reticulum germ centers and follicles are involved in the process, and there is no invasion of the capsule by the lymphocytes of the nodes. There is a great variation in the degree of involvement of the different constituents of the nodes even in different parts of the same nodes. (Further details will be found in the section devoted to the pathologic picture.)

There is a great deal of similarity between the onset, causation and mechanism of the pharyngeal symptoms and the glandular involvement in cases of infectious mononucleosis and in cases of definitely proved nonspecific mesenteric adenitis beginning with infection of the throat and cervical glands in which the characteristic hematologic factors are not present.

The complex described by Pirera<sup>127</sup> is probably very similar to the ordinary forms of infectious mononucleosis except that no changes in the blood were described. Pirera expressed the belief that the disease is caused by a lymphotropic virus which he assumed to be like that which causes Pfeiffer's glandular fever. I have no knowledge of this complex and simply mention it for what it is worth.

*From the "Rheumatic" Group of Diseases.*—Lymphadenopathy of one kind or another occurs in many of the groups of illnesses which have been linked together under the rather vague designation "rheumatic group" (acute rheumatic fever, tonsillitis, chorea, polyarthritis, erythema, purpura, etc.). In many of these conditions streptococci of one kind or another are found, and this is probably the most important reason (besides the clinical manifestations) why these groups have been associated.

(a) Acute Rheumatic Fever: Rather characteristic abdominal pain occurs frequently (the incidence is 20 per cent, according to Coburn<sup>128</sup>)

123. Nolan, R. A.: Report of So-Called Epidemic of Glandular Fever (Infectious Mononucleosis), U. S. Nav. M. Bull. **33**:479 (Oct.) 1935.

124. Bernstein, A.: Infectious Mononucleosis, *Medicine* **19**:85 (Feb.) 1940.

125. Bradshaw, R. W.: Mitral Stenosis Following Infectious Mononucleosis, *Ohio State M. J.* **27**:717 (Sept.) 1931.

126. Pratt, C. L. G.: The Pathology of Glandular Fever, *Lancet* **2**:794 (Oct. 10) 1931.

127. Pirera, A.: Una nuova adenolinfopatia acuta o un nuovo tipo di "febbre ghiandolare"? *Rinasc. med.* **14**:151 (March 15) 1937.

128. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931; Relationship of the Rheumatic Process to the Development of Alterations in Tissues, *Am. J. Dis. Child.* **45**:933 (May) 1933; Observations on the Mechanism of Rheumatic Fever, *Lancet* **2**:1025 (Oct. 31) 1936.

in patients with acute rheumatic infection, and not uncommonly it is the presenting symptom, especially in children. Such patients often are thought to have acute intra-abdominal surgical conditions, with appendicitis most frequently suspected. Giraldi<sup>129</sup> divided his patients into three groups: those with vague gastrointestinal disturbances; those with symptoms suggesting appendicitis, and those presenting a picture of diffuse peritonitis. In those operated on, nothing may be found or there may be slight increase in serous peritoneal fluid, with, perhaps, fibrin flakes and slight injection of the appendical region or enlargement of the mesenteric lymph nodes.

Postmortem examination (Paul;<sup>130</sup> Klinge;<sup>131</sup> Holsti;<sup>132</sup> Pappenheimer and von Glahn<sup>133</sup>) shows specific rheumatic nodules in the peritoneum, arteritis in the intestine, purpura with subperitoneal hemorrhage and enlargement of the mesenteric glands.<sup>109</sup>

Michelazzi<sup>134</sup> found that there is an intense reaction of the germinal centers of the lymphatic follicles with proliferation of the reticuloendothelial cells, subcapsular and intracapsular plasma cell infiltration, catarrh of the sinuses of the nodes, proliferation of the endothelial walls of the glandular sinuses, increase of the argentophil cells of the lymphatic cords and of the sinuses of the nodes and intravascular alterations of a granulomatous type. The pathologic alterations are identical or similar to those which take place in the course of rheumatic fever, in certain forms of chronic rheumatism with splenomegaly and in the lymph nodes and the spleen in the presence of acute polyarthritis. According to Michelazzi,<sup>134</sup> the disease of the lymph nodes in "rheumatic" diseases is independent of the chronic, acute or subacute types of "rheumatism." It is due to a general pathologic condition of the reticuloendothelial system which involves, selectively, the para-

129. Giraldi, J. J. J.: Abdominal Symptoms in Acute Rheumatism, *Arch. Dis. Childhood* **5**:379 (Dec.) 1930.

130. Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, *Medicine*, **7**:383 (Dec.) 1928; *The Epidemiology of Rheumatic Fever*, printed for the American Heart Association, 1930; Localized Peritonitis in Rheumatic Fever, *Bull. Ayer Clin. Lab., Pennsylvania Hosp.* **2**:9, 1930.

131. Klinge, F.: *Der Rheumatismus*, Munich, J. F. Bergmann, 1933.

132. Holsti, O.: Zur Kenntnis der Arteritis verrucosa, *Arb. a. d. path. Inst. d. Univ. Helsingfors* **5**:110, 1927; *Beiträge zur Kenntnis der entzündlichen Klappenaffektionen mit besonderer Berücksichtigung der Pathogenese*, *ibid.* **5**:401, 1928.

133. Pappenheimer, A. M., and von Glahn, W. C.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, *Am. J. Path.* **2**:235 (May) 1926.

134. Michelazzi, A. M.: Osservazioni sulla ghiandola linfatica nel reumatismo cronico primitivo, *Minerva med.* **2**:609 (Dec. 9) 1937.

articular lymph nodes of the rheumatic joints and sometimes also the bone marrow and the spleen.

(b) Erythematous Conditions: A severe and often fatal form of purpura has been referred to previously as a late complication of the common exanthemas (scarlet fever and measles). Other forms of the purpuric type of symptom complex (erythema multiforme, Henoch's purpura, Osler's visceral crises of the erythema group) occur also. These, too, have been related in an indefinite manner to the "rheumatic" group. I give the notes of a pertinent case which occurred among my earliest experiences:

An adolescent girl was admitted to the hospital with fever, abdominal pain, vomiting and the local physical signs of an acute process in the right lower abdominal quadrant. Moderately severe acute appendicitis was immediately assumed to be present, and the patient was subjected forthwith to a laparotomy. The exploration showed a normal appendix; diffuse marked edema of the terminal portion of the ileum without apparent sign of any intrinsic lesion of the bowel wall, and a moderate number of enlarged mesenteric lymph nodes. The appendix was removed. The rest of the lesion was not disturbed because I suspected that this might be one of the visceral crises, in which, at that time, I happened to be particularly interested.

No rash had been noticed on the patient's body before operation, and this was corroborated by another observation as soon as the operation was completed. Nevertheless, on the very next morning there was typical erythema multiforme scattered over the extensor surfaces of both the knees and the elbows. A thoroughly compensated and symptomless chronic endocarditis of the "rheumatic" type was also present.

The patient made an otherwise uneventful convalescence.

(c) Polyarthritis: Usually correlated with the "rheumatic" group is a form of polyarthritis which is common in children and occurs occasionally in the aged. There is usually a marked generalized reaction, with fever, palpable lymph glands, a large spleen and liver, anemia and wasting. The pathologic tissue changes are similar in adults and in young children, and in far advanced forms of this disease amyloid degeneration of various organs may be seen. Some of the cases have been isolated and are distinguished as examples of a separate entity occurring in children under the name of Still's disease and in adults under the heading of Felty's syndrome.

The bacterial cause usually found is a streptococcus and the agglutination phenomena are usually most marked with the serums of adults affected with rheumatoid arthritis. In cases of acute involvement in children positive blood cultures are sometimes obtained (Margolis and Dorsey<sup>135</sup>). The most tenable conclusion at present is that these forms

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135. Margolis, H. M., and Dorsey, J.: Bacteriology of the Blood in Chronic Infectious Arthritis, *J. Infect. Dis.* 46:442 (June) 1930.

of polyarthritis are due to a streptococcus infection and that possibly some virus is associated with them. In correlating these cases in general medical practice the best possible assumption at present is that the disease is a general infection in which the organism has a predilection for articular involvement.

The enlarged glands show subacute inflammation, mild fibrosis, lymphocytic infiltration and small areas of hemorrhage. In spite of the fact that they are usually related to the affected joints, the following observations are worthy of consideration:

1. A remarkable fact about polyarthritis is the frequency with which in clinical practice one encounters it combined with or interpolated between various other manifestations of the diverse complexes usually associated in the "rheumatic" group. The facility with which these various symptom complexes can be present in the same person in various sequences and combinations is also a characteristic of the "rheumatic" group.

2. Many of the conditions to which reference has been previously made in this communication as regards abdominal lymphadenopathy can also be associated with or followed by polyarthritic manifestations. Acute arthritis follows scarlet fever in about 10 per cent of the cases; typhoid fever occasionally, and bacillary dysentery frequently. In about one half of the cases undulant fever is followed by "rheumatic" forms of arthritis. This gives one a lead for the explanation of the aches and pains referred to the bones and joints which are such essential features of influenza, abdominal grip and infections of the upper respiratory tract.

3. The frequency with which an infection of the upper respiratory tract or of the throat is a preceding or originating factor in so many of these conditions is noteworthy.

4. The most common and most frequently demonstrable etiologic agent present in all of these conditions is a streptococcus. And streptococci are so constantly harbored in the oropharynx as to be almost normal inhabitants.

5. The frequency with which swelling of the lymph glands occurs in all of these symptom complexes is noticeable. Sometimes the lymphadenopathy is demonstrably generalized. Sometimes the diminishing range of involvement from the regional cervical area through the axillas and groins indicates how the infecting agent has entered and by which path it has progressed throughout the body and permits the assumption also of any abdominal involvement of equal magnitude. Sometimes limitation to the abdominal area indicates an entrance of the infecting agent through the abdominal portion of the alimentary canal.

PATHOLOGIC PICTURE <sup>109</sup>

*General Considerations.*—It is difficult to estimate the frequency with which the wear and tear of life produces or results in enlargements of the intra-abdominal nodes. If one is to judge from similar enlargements of the lymph nodes in other regions of the body, one would expect the frequency to be relatively high, and this would seem to be corroborated by Still's <sup>136</sup> experience, in which 59 per cent of children examined post mortem for any and all conditions had enlarged mesenteric glands. On the other hand, my own experience, based on intra-abdominal operations done in hundreds of cases for any and all kinds of disease, leads me to believe that nonspecific enlargements of the mesenteric glands in children are rare except when one is dealing with this form of nonspecific mesenteric adenitis or when tuberculous glands are present. And under modern conditions tuberculous infection is becoming less and less prevalent. I am quite sure that in our American environment this must be the experience of most surgeons.

I refer to an interesting observation of Pribram's <sup>137</sup> in regard to the interrelation of glandular swelling and the corresponding preceding lesion. According to Pribram,<sup>137</sup> Winkler's <sup>138</sup> statistics, covering 300 cases of intestinal tuberculosis, are remarkable for the fact that the presence or degree of intestinal ulceration was in inverse proportion to the presence and degree of enlargement of the mesenteric glands. This series undoubtedly includes cases in which the tuberculous element was not definitely proved. Pribram <sup>137</sup> noted also the same thing in acute conditions of the gallbladder—that the number of glands swollen and the degree of swelling were usually in inverse proportion to the degree of inflammation of the gallbladder. According to my own observation, the extent and degree of mesenteric glandular enlargement in the simple form of nonspecific mesenteric adenitis is also in inverse relation to the degree of demonstrability of any preceding intra-abdominal lesion; as a matter of fact, no other lesion is usually demonstrable. Note how frequently also a similar relation is present in cases of cervical adenitis.

*Factors Leading to Nonspecific Mesenteric Lymphadenopathy.*—These may be grouped as follows: (1) jejunoileal lesions; (2) lesions

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136. Still, G. F.: *Common Disorders and Diseases of Childhood*, ed. 3, New York, Oxford University Press, 1915, p. 424.

137. Pribram, B. O.: *Die Lymphangitis mesenterialis als abdominelle Herdinfection, Substrat der peritonealen Adhäsionen und Bindeglied zwischen den sogenannten zweiten Krankheiten*, Arch. f. klin. Chir. **160**:362, 1930; *Nabelkolik, lymphangitische Form der Appendizitis und Lymphangitis mesenterialis*, München. med. Wchnschr. **82**:942 (June 14) 1935; *Das Krankheitsbild der Lymphangitis mesenterialis und peritonealis*, Med. Klin. **27**:871 (June 12); 911 (June 19) 1931.

138. Winkler, cited by Pribram.<sup>137</sup>



of the vermiform process; (3) lesions of the cecum, and (4) infections of the blood stream.

*Distribution of Lymphadenopathy.*—In general, lymphadenopathy occurs as follows:

1. As a generalized condition in which all the glands are involved, although even here one can distinguish that one group of glands are apparently more involved than the others.

2. As an initial involvement of one regional group of glands, other regional groups of glands being involved subsequently.

3. As an involvement of one regional group without apparent spread to or from any other group.

*Types of Lesions.*—The forms of nonspecific mesenteric adenitis discussed in this communication belong in the last two groups. It is noteworthy that the glands are involved as a regional manifestation except in those cases in which infection at the upper end of the alimentary tract precedes the abdominal manifestations. In a minority of these, swelling of the cervical glands is noted to occur either prior to the onset of the abdominal symptoms or one gets the impression—which is not often susceptible of corroboration—that the two groups of glands become involved simultaneously. Curiously enough, the combination of cervical and mesenteric lymphadenopathy is never associated with similar swelling of lymph glands in other regional groups, with the possible exception of the mediastinal.

There is no doubt, however, that some of the conditions under discussion are, or begin as, generalized lymphadenopathy (group 1). I can remember several of my earliest cases; the patients were young children in whom the sudden onset of abdominal symptoms compelled a concentration of observation on the abdomen and in whom, on reexamination, generalized enlargement of the lymph nodes was present.

The observed lesion in cases of simple mesenteric adenitis usually shows nothing beyond simple hyperplasia, confirming the fact that all parts of the glands are in active reaction to the cause of the inflammation and swelling, whatever it may have been.

Curiously enough, in some of the conditions described in this paper a somewhat more definite picture is observed. In the case described by Barker and Wood<sup>60</sup> and already cited, in which lymphadenopathy occurred as a complication of acute iodism during treatment of hyperthyroidism, the lymph node picture was described as follows:

The lymph nodes showed hyperplasia of the lymphoid tissue and some fresh hemorrhages. The sinuses contained an abundance of mononuclear cells. Peculiar miliary inflammatory perivascular lesions were present in the majority of tissues; in the lymph nodes and spleen these usually occupied the position of the germinal centers.

They consisted mainly of mononuclear cells; and in most of the lesions there were lymphocytes and a few eosinophils. Often there were epithelioid cells arranged as they are in tubercles, and in many of the organs some lesions contained typical Langerhans giant cells. Certain of the lesions, especially in the spleen, showed a central area of necrosis. No spirochetes were demonstrated by dark field examination or in stained smears; neither tubercle bacilli nor other bacteria were found in any of the lesions. The nature of these lesions was obscure.

In the regional lymphadenopathy which Hadfield<sup>139</sup> described as occurring with regional ileitis, a somewhat similar pathologic picture was observed.

In the regional lymph-nodes a clear-cut specific formation of giant-cell systems identical with that found in the thickened submucosa is present. Some of the section showed as many as 20 to 30 foci of non-caseating giant cell systems, while other glands did not show any; and as the lesions grew older these giant cell systems were *more and more difficult to find and were replaced by a picture of a simple non-specific lymphadenitis*.

Viewed as isolated and static histologic pictures, the giant cell systems in the glands and in the bowel wall were indistinguishable from those of tuberculosis, but their tendency to retrogress without excessive scarring and the absence of caseation and acid-fast bacilli contradicted this.

A somewhat similar picture, associated with the appearance of large cells, has also been demonstrated in cases of the lymphadenopathy which accompanies scarlet fever (Schlegel<sup>140</sup>).

In cases of infectious mononucleosis the microscopic appearance of lymph nodes varies with the stage and intensity of the disease when the lymph nodes are examined. Longcope<sup>141</sup> noted the occasional presence of large epithelioid cells. Pratt's<sup>142</sup> two observations of the same patient, one during the acute stage and a second a year later, showed the usual forms of hyperplasia; early degenerative changes in the vessel walls, hemorrhages and marked reticuloendothelial proliferation with some central necrosis, all of which obliterated all lymphoid elements.

Curiously enough, in these three forms of disease lymphadenopathy is associated with severe infection of the alimentary canal accompanied with necrosis. Whether this peculiar anatomic picture in the lymph nodes has something to do with the intensity of the process in the corresponding part of the alimentary canal is something which must be,

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139. Hadfield, G.: The Primary Histological Lesion of Regional Ileitis, *Lancet* 2:773 (Oct. 7) 1939.

140. Schlegel, cited by Henke and Lubarsch.<sup>72</sup>

141. Longcope, W. T.: Infectious Mononucleosis (Glandular Fever) with a Report of Ten Cases, *Am. J. M. Sc.* 164:781 (Dec.) 1922.

142. Pratt, J. H.: Purpura and Hemophilia, in Osler, W.: *Modern Medicine*, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 5, p. 101.

for the present, assumed. As in the much milder form of nonspecific adenitis, only a hyperplastic condition is present in the lymph nodes, indicating a correspondence of intensity of process between the lymph node picture and the picture in the intestinal tract, it must be assumed that the differences in the anatomic picture are caused by the different gradations of toxicity of the etiologic agent.

It is interesting to note that in these conditions the impossibility of demonstrating the presence of any tubercle compels the assumption that the lesions are definitely not tuberculous. One must also assume that the so-called "tubercle" arrangement can be found not only in specific forms of infection, such as tuberculosis and syphilis, but in nonspecific forms to which at present no definite cause can be assigned. It may well be that this sort of picture represents the anatomic progression between the simple forms of lymphadenopathy and those associated with definitely specific anatomic pictures, which are customarily correlated with syphilis and especially with tuberculosis. Undoubtedly this also explains the classification, not only in the earliest period of knowledge of this subject but later, of all forms of enlargement of the mesenteric glands as tuberculous.

Mixed infection in cases of tuberculous adenitis plays a very important role. It is commonly noted in the neck. Less frequently it is observed in the abdomen.

Head<sup>143</sup> reported a case of tuberculous mesenteric lymphadenitis in which secondary infection and rupture occurred. He found 2 similar cases reported in the literature.

Undoubtedly there must be many similar cases in the available experience. In the presence of such mixed infections the anatomic picture sometimes is vague enough to make it difficult to say definitely whether the infection is originally tuberculous even though from clinical experience one may feel fairly sure that it is. Mixed infection of tuberculous glands is commonly severe enough to cause sufficient destruction to wipe out a good deal of the glandular structure, so that the original tuberculous formation cannot be visualized. Again, I should like to point out the similarity between the conditions occurring in the cervical region and those occurring in the mesenteric area.

#### COMPLICATIONS

Occasionally the glands break down and abscesses are formed. That the glands may become involved secondarily or may continue to enlarge progressively for a time after any preceding intestinal lesion has healed,

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143. Head, J. R.: Tuberculosis of the Mesenteric Lymph Glands, *Ann. Surg.* 83:622 (May) 1926.

even to the point of abscess formation, is probable enough and is exactly analogous to what happens in the neck in cases of secondary adenitis of the cervical and retropharyngeal lymph glands following a pharyngeal, a postnasal or an oropharyngeal infection.

Cases of abscess formation from mesenteric lymph glands have been described by Nyström,<sup>144</sup> Polya,<sup>145</sup> Borchard,<sup>146</sup> Doyen,<sup>147</sup> Johnsson-Breuer,<sup>148</sup> Hahn and me,<sup>4b</sup> Etchegorry<sup>149</sup> and Calvanico.<sup>150</sup>

Ybarz<sup>151</sup> distinguished five principal types of lesions:

1. Solitary enlarged lymph glands ranging from the size of a hazelnut to that of a hen's egg. The mass is usually fluctuating and contains, as a rule, fluid pus.

2. Multiple lymph glands which appear enlarged and edematous. Usually one of them is the seat of abscess formation.

3. Multiple involvement of the lymph glands showing confluence. The suppuration of the mass usually gives rise to multiple abscess formation.

4. Multiple involvement of solitary lymph glands which present merely hypertrophy but which on sectioning are found to contain multiple microabscesses.

5. Lesions bearing grossly a striking resemblance to neoplastic formations.

Suppuration of the mesenteric lymph glands may lead to the following processes and complications:

1. Massive invasion of the entire mesenteric lymphatic gland system.

2. Suppurative periadenitis followed by an infiltration of the mesentery or of the mesoappendix. In this condition the mesentery becomes markedly thickened.

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144. Nyström, G.: Studies of the Results of Treatment of Appendicitis at the Akademiska Sjukhuset in Uppsala (Surgery), *Nord. med. ark. (supp.)* **7**:1, 1907.

145. Polya, E.: Untersuchung über die Lymphbahnen des Wurmfortsatz und des Magens, *Deutsche Ztschr. f. Chir.* **69**:421, 1903.

146. Borchard, A.: Die primäre Lymphangitis des Wurmfortsatzes, *Deutsche med. Wchnschr.* **54**:1075 (June 29) 1928.

147. Doyen, cited by Strömbeck.<sup>97</sup>

148. Johnsson-Breuer, cited by Strömbeck.<sup>97</sup>

149. Etchegorry, P. A.: Linfadenitis mesenterica supurada, *Semana méd.* **1**: 990 (April 21) 1927.

150. Calvanico, R.: Le modificazioni dell'apparato linfo-adenideo local dell'appendicite, *Policlinico (sez. chir.)* **34**:253 (June) 1927.

151. Ybarz, P. L.: Adenitis supuradas del mesenterio, *An. Fac. de med. de Montevideo* **23**:531, 1938.

Moore<sup>152</sup> reported the following case:

A 42 year old woman was sick for two weeks with "appendicitis," chills, high fever, sweats, abdominal distention and moderate tenderness. No mass was palpable. At operation the appendix and the pelvic organs appeared normal. To the left of the spine a fluctuating mass was present between the folds of the mesentery, which was taken to be of glandular origin. Drainage was established. Death occurred a few days after operation. The origin of the infection was not determined.

### 3. Localized peritonitis.

4. Purulent or fibrinopurulent peritonitis of various degrees of severity determined by the rupture of an intralymphatic abscess or by the propagation of an adjacent suppurative process.

The following case is taken from a report by Pribram<sup>137</sup> and illustrates the especially virulent form of mesenteric adenitis.

A severe pharyngeal infection with enlargement of the cervical glands developed in a 29 year old man and was quickly followed by generalized acute abdominal pain with nausea and high fever. The physical signs were those of peritoneal irritation or peritonitis, and during a laparotomy, which was done forthwith, the abdominal organs (including the appendix) were found to be relatively normal. There was, however, a moderate amount of peritoneal exudate; the glands in the mesentery were apparently much increased in number and much swollen, and the glandular involvement extended high up in the ileocolic chain to the level of the cystic and cholecystic lymph glands. The postoperative course was marked by pyloric ileus, for which an ileostomy was done, and the patient died shortly thereafter.

The postmortem examination showed the enlarged, inflamed glands, but apparently it was not possible to demonstrate a rupture of any peritoneal abscess.

Pribram expressed the opinion that this was similar to what is already called primary peritonitis of unknown origin.

5. Intestinal occlusion, determined either by pressure or by the formation of adhesions.

6. Formation of a tumor-like mass situated usually in the ileocolic recess or at the root of the mesentery. This lesion may be so small as to escape detection during clinical, surgical or postmortem examination.

The following notes are from my own experience:

For an acute abdominal episode which was taken to be acute appendicitis a man of 23 underwent surgical exploration. The appendix was apparently normal, but the glands in the ileocecal angle were all enlarged. An uneventful convalescence and recovery followed. About one year later there developed signs of acute intestinal obstruction, and an indefinite mass could be felt in the right iliac fossa, directly behind the scar of the previous operation. During the exploration the cause of the obstruction was found to be a large inflammatory mass in the angle of junction of the ascending colon and the small intestine, containing a small focus of suppuration. The coils of the intestine were all matted together. It was

152. Moore, J. E.: Infection of the Retroperitoneal Lymphatics, Surg., Gynec. & Obst. 15:30, 1912.

not possible to do anything except drain the abscess and establish an enterostomy on the proximal side of the mass. The patient died, however, about twenty-four hours later, from diffuse peritonitis.

7. Cyst formation with subsequent absorption, which may be so complete as to leave little or no trace of the original lesion.

8. Subphrenic abscess.

9. Extension into the liver with the formation of multiple hepatic abscesses.

The notes on the following case were given by Lenhartz.<sup>153</sup>

A 23 year old working man was sick for ten days with increasing abdominal pain and temperature. Physical examination showed a tender belly, with marked spasm in the right lower quadrant. There was no enlargement of the liver. The heart and lungs were normal. Rectal examination gave negative results. During the next two weeks the clinical picture increased at first and then retrogressed. On the fifteenth day after the patient's admission to the hospital there was a sudden chill, followed by a rise in temperature and an exacerbation of abdominal pain. The increase of symptoms was progressive and was accompanied with increased distention and tenderness of the abdomen. Two weeks later the area of hepatic dulness had enlarged upward. One week thereafter an abscess of the liver was drained. The blood culture was negative. Spreads from the hepatic abscess showed bacilli and streptococci. The patient died one week thereafter.

The postmortem examination showed an entirely normal cecum, generalized purulent peritonitis and a great number of calcified mesenteric glands. A retroperitoneal abscess was present, which was definitely said to be due to an infected, suppurating ruptured calcified gland, and there was a communication with the neighboring coil of jejunum. There was a large abscess in the liver.

#### PORTAL OF ENTRY<sup>154</sup>

*Appendix.*—As a portal of entry of the causative agent into the abdominal glands in nonspecific mesenteric adenitis, the appendix has probably received the most attention and was concluded to be the most probable site of the initial lesion by Brown,<sup>155</sup> Pribram,<sup>137</sup> Coleman,<sup>75</sup> Royster,<sup>59</sup> Short,<sup>5</sup> Lamson,<sup>156</sup> Freeman,<sup>2</sup> Speese and Klein,<sup>73</sup> Segar and

153. Lenhartz, H.: Die septischen Erkrankungen, Vienna, A. Hölder, 1903.

154. Andersen, K.: Universal Mesenterial Lymphadenitis Simulating Appendicitis, Med. rev., Bergen **36**:528, 1919. Bagg, K.: Die "Appendicitisähnliche" isolierte Mesenterialdrüsentuberkulose und ihr Schicksal im weiteren Verlaufe, Beitr. z. klin. Chir. **141**:23, 1927. Brown, A. E.: Ileocaecal Lymphadenitis in Children, Surg., Gynec. & Obst. **65**:798 (Dec.) 1937. Hertel, E.: Lymphadenitis mesenterialis (Lymphadenitis mesenterialis), Beitr. z. klin. Chir. **166**:231, 1937. McFadden, C. D. F.: Mesenteric Adenitis and Its Clinical Manifestations, Brit. M. J. **2**:1174 (Dec. 24) 1927. Parker, D. W.: Tuberculous Mesenteric Glands Simulating Appendicitis, Boston M. & S. J. **167**:915-918, 1912.

155. Brown, H. P.: Acute Mesenteric Adenitis Simulating Appendicitis, S. Clin. North America **9**:1195 (Oct.) 1929.

156. Lamson, O. F.: Mesenteric Lymphadenitis and Acute Appendicitis, S. Clin. North America **9**:1195-1196 (Oct.) 1929.

Rosenak<sup>157</sup> and others. The available information in favor of this hypothesis is as follows:

Quénu<sup>158</sup> and Marchant<sup>159</sup> found changes in some of the appendixes which they removed but not in all. They gave no details of the anatomic characteristics. Goldberg and Nathanson<sup>78</sup> found hyperplastic changes of the appendicular lymphadenoid tissue in many of the cases and other changes in only 2 cases.

Strömbeck<sup>97</sup> observed microscopic changes in the appendix in 27 of his 39 patients with mesenteric lymphadenitis.

In 8 of the cases in Ireland's<sup>33</sup> series there was evidence of pathologic change. In 1 there was hypertrophy of the lymphoid follicles; in 4, acute inflammation; in 1, subacute inflammation; in 1 there were infection with *Oxyuris vermicularis* and focal infiltration with polymorphonuclear leukocytes and eosinophils, and in 1 there was focal ulceration confined to the submucosa.

These are the main anatomic and pathologic arguments in favor of the appendical portal of entry for mesenteric adenitis. Many of the observers did not support their contention by solid anatomic or other evidence; one has the feeling that many of these observations are mere unsupported assumptions and that the "post hoc, ergo propter hoc" type of reasoning in clinical observation has been allowed to take the place of more solid scientific methods. On the other hand, the available information which would tend to discredit the appendical portal of entry of mesenteric adenitis has a more solid foundation. This available knowledge is as follows:

Every inflammatory process of the vermiform appendix is accompanied with demonstrable lesions of its corresponding mesenterium, the lesions varying from case to case and according to the type of appendicitis. In general, the severity of these lesions is proportional to the intensity of the anatomicopathologic process occurring in the wall of the vermiform process.

In the acute phase of appendicitis the reactions in the mesenterium include edema, exudation, infiltration, lymphangitis, rigid mobilization of the reticuloendothelial elements and perivascular infiltrations. With severe involvement there are impairment of the circulation and thrombosis of the venous radicles, which may lead to purulent mesenteric thrombophlebitis and hepatic abscess (Beluffi<sup>160</sup>).

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157. Segar, L. H., and Rosenak, B. D.: Non Tuberculous Mesenteric Lymphadenitis in Childhood, *Am. J. Digest. Dis. & Nutrition* 2:356 (Aug.) 1935.

158. Quénu, M.: De l'adénopathie mésentérique dans les appendicites aiguës toxiinfectieuses, *Bull. et mém. Soc. de chir. de Paris* 28:540, 1902.

159. Marchant, G.: Adénite dans l'appendicite, *Bull. et mém. Soc. de chir. de Paris* 26:77, 1900.

160. Beluffi, E. L.: La mesenteriolite appendicolare, *Arch. ital. di chir.* 48:697, 1938.

On anatomic grounds no swelling of the mesenteric lymph nodes should take place, because the path of lymphatic drainage on the one side is upward in the retroperitoneal lumbar region toward the subphrenic space, and on the other side the lymphatic drainage of the appendix is normally limited and is related anatomically to that of the large intestine. It does not, as a rule, drain into the mesenteric glands in the ileocolic junction. The group of lymph nodes normally found in the ileocolic angle of the mesentery are anatomically and physiologically related to the small intestine, especially to its distal half, i. e., the ileum. (Compare with the section on the anatomy of the mesenteric lymph nodes.)

The lymphatics of the appendix <sup>161</sup> are associated with those of the cecum. Polya <sup>145</sup> and later Jamieson and Dobson <sup>162</sup> showed that a few lymph vessels arising at the base of the appendix pass around each side of the cecum to terminate in the nodes of the ileocolic chain, either directly or by the intermediation of the anterior or posterior cecal nodes. The lymphatic network of the appendix usually follows the branches of the appendical artery by a number of trunks, one of which may traverse a lymph nodule sometimes contained in the mesoappendix (not constant). The remainder terminate in the inferior nodes of the ileocolic chain or in the posterior cecal nodes, but sometimes one of these collecting trunks may reach nodes on the ileocolic chain as high as the third part of the duodenum. One may also see a cecal lymphatic penetrate the mesoappendix to reach an appendical or an ileocolic lymph node.

On the basis of extensive clinical experience many observers (Hahn and I; <sup>4b</sup> Carson; <sup>163</sup> Goldberg and Nathanson <sup>78</sup>) have previously

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161. Aschoff, L.: *Die lymphatische Organe*, Berlin, Urban & Schwarzenberg, 1926. Auguy, J.: *De l'adénopathie appendiculaire*, Thesis, Lyon, no. 134, 1901. Kleiber, N.: *Erfahrungen über die Lymphangitis mesenterialis*, Thesis, Berlin, 1935. Levin, O. A.: *Die Mesenteriolitis, ihr Bedeutung für die Symptomatologie, Diagnostik und Klinik der Appendizitis und ihrer Komplikationen: Histologische und klinische Untersuchungen*, Beitr. z. klin. Chir. **160**:491, 1934. Losifov, G. M.: *Das Lymphgefäß-System des Menschen*, Jena, Gustav Fischer, 1930. Most, A.: *Chirurgie der Lymphgefäße und der Lymphdrüsen*, in von Bruns, P.: *Neue deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1917, vol. 24, pp. 41-47; *Die Topographie des Lymphgefäßapparates des menschlichen Körpers*, Stuttgart, E. Schweizerbart, 1908; *Bibliotheca medica*, Cassel, T. G. Fischer & Co., 1908, pt. C, no. 21. Zapel, E.: *Ueber die Frage der Mesenteriolitis appendicularis und der postappendicitischen Veränderungen des Venenlymphsystems*, Arch. f. klin. Chir. **169**:180, 1932.

162. Jamieson, J. K., and Dobson, J. F.: *The Lymphatic System of the Stomach*, Lancet **1**:1061, 1907; *The Lymphatic System of the Caecum and Appendix*, *ibid.* **1**:1137, 1907.

163. Carson, H. W.: *On the Clinical Aspects of Tuberculous Mesenteric Glands*, Lancet **1**:869 (June 22) 1935.



expressed the belief that the appendix has no clinical relation to mesenteric adenitis. This is supported by the fact that the appendix in the vast majority of the cases is uninvolved in acute mesenteric adenitis; by the fact that in bona fide acute appendicitis of various grades and types the mesenteric glands are not enlarged or inflamed, and by the anatomic facts (*a*) that the appendix is part of the large bowel; (*b*) that the lymphatic drainage of the appendix is a limited and local one; (*c*) that in mesenteric adenitis the glands are diffusely involved (Freeman<sup>2</sup>), and (*d*) that those which are involved drain anatomically the small intestine and especially its ileal portion.

One cannot escape the fact mentioned, that appendicitis is not generally accompanied with gross swelling of the mesenteric lymph nodes. My own experience coincides with that of Ireland,<sup>33</sup> who said that if inflammation of these nodes occurs in all cases of appendicitis it is not so grossly evident at operation and would therefore have to be discovered on microscopic examination. There is no report in the literature of the routine sectioning of the mesenteric glands in any large series of cases of acute appendicitis. But my own laboratory experience of early years and my own subsequent surgical experience and that of many other surgeons testify to the absence or extreme rarity of the relation of acute appendicitis and inflammatory enlargement of the mesenteric lymph nodes.

Yet it seems demonstrable that an occasional case occurs in which swellings of the mesenteric glands follow acute appendicitis. The following notes on a recent personal experience seem to confirm this.

In a 16 year old girl with a typical history of acute appendicitis of twenty-four hours' standing and without a history of any preceding infection of the upper respiratory tract, abdominal exploration revealed an appendix which showed the slightest degree of inflammation on its external coat. The interior of the appendix was filled with fluid pus and showed a more marked degree of inflammation. Several moderately swollen glands were visualized and palpated in the ileocecal angle of the mesentery. The appendix was removed, and the patient made an uneventful recovery.

There was no other glandular enlargement in this patient, and there was no history of any such enlargement or of any form of lymphatic disease.

The explanation is based on abnormal anatomic arrangements in the lymphatic apparatus and drainage.

Abnormal lymphatic connections of the appendix have been observed and described by Clade,<sup>48</sup> Cohn,<sup>164</sup> Walter-Sallis,<sup>165</sup> Français and

164. Cohn, M.: Der Verlauf der appendiculären Lymphgefäße, *Arch. f. Anat. u. Entwicklungsgesch.*, 1905, p. 445.

165. Walter-Sallis, J.: Le foie dans l'appendicite, *Rev. de chir.* 49:181 and 649, 1914.

Moure,<sup>166</sup> Lockwood,<sup>167</sup> Poirier and Cunéo,<sup>168</sup> Polya,<sup>145</sup> Jamieson and Dobson,<sup>162</sup> Bartels,<sup>169</sup> Bercéanu,<sup>170</sup> Franke,<sup>49</sup> Descompes and Turnesco,<sup>44</sup> Pellé and Pellé,<sup>171</sup> Braithwaite<sup>172</sup> and others. Connections have been described into the retroperitoneal lymphatics to the perirenal space and the liver and downward into the pelvis and the pelvic organs (the latter, however, are denied). For the subject under discussion it is important to know that there are, as abnormal variations of the normal, lymphatic vessels which on their way to the liver pass across the mesoappendix and the mesentery directly (Walter-Sallis<sup>165</sup>) or indirectly and in a retrograde manner through the mesenteric and celiac glands. According to Lockwood,<sup>167</sup> the appendical lymphatics may also be in connection with the lymph nodes of the mesocolon.

This is the anatomic explanation of the occasional case in which enlargement of the mesenteric lymph glands follows acute appendicitis and for the failure to observe any lymph node enlargement with the vast majority of the ordinary types of acute appendicitis (catarrhal, suppurative, gangrenous, etc.). The physiologic explanation is just as important, in that the normal lymphatic current from the appendix is not inward toward the mesentery but upward retroperitoneally, behind to the colon and in the lumbar gutter toward the liver and subphrenic space. This is my own experience as well as that of many other observers. If swollen mesenteric glands with acute appendicitis have been observed by others, they occur under some abnormal stress; the explanation would have to be made either on the ground that the acute appendicitis was only part of a larger lesion, the extra-appendicular part of which caused the lymphadenopathy, or on the ground that an anatomic variation was present which permitted or, rather, compelled the lymphatic drainage from the appendix along unaccustomed paths by the anastomosis with the lymphatics which normally drain the ileum. The physiologic purpose of the anatomic arrangement is ordinarily a powerful factor in preventing an appendical portal of entry for the causative agent of mesenteric adenitis.

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166. Français and Moure: Appendicite aiguë avec abcès multiples du foie, Bull. et mém. Soc. anat. de Paris **83**:458, 1908.

167. Lockwood, C. B.: Note upon the Lymphatics of the Vermiform Appendix, J. Anat. & Physiol. **34**:9, 1899.

168. Poirier, P., and Cunéo, B.: Les lymphatiques, in Poirier, P., and Charpy, A.: *Traité d'anatomie humaine*, Paris, Masson & Cie, 1902, vol. 2, pt. 4.

169. Bartels, P.: *Das Lymphgefäß-system*, Jena, Gustav Fischer, 1909.

170. Bercéanu, D.: Les relations lymphatiques entre l'appendice et la région duodéno-pancréatique, Rev. de chir., Paris **69**:421, 1924.

171. Pellé, A., and Pellé, A. (Mme.): Lymphatiques de la trompe, Ann. d'anat. path. **8**:509 and 605, 1931.

172. Braithwaite, L. R.: Tuberculosis of Glands in the Ileo-Caecal Angle: A Cause of Pain in the Right Iliac Fossa, Brit. J. Surg. **13**:439 (Jan.) 1926.

Experience with the operative results of appendectomy performed in the presence of acute mesenteric adenitis has been used in a controversial manner by each side of the contention. One wonders why the removal of such innocent-looking appendixes as are found in the vast majority of the cases should produce such a large percentage of symptomatic cures without later recurrence of symptoms. In my own experience, recovery after appendectomy has occurred always, and in patients examined in the follow-up clinics no recurrence of symptoms has been observed. This was also the experience of Royster,<sup>69</sup> Brown<sup>163</sup> and others. In Marshall's<sup>77</sup> series of 26 patients, approximately 85 per cent showed similar results, and in Strömbeck's<sup>97</sup> series 87 per cent of patients were free from symptoms postoperatively. Recurrences of symptoms have thus occurred in approximately 15 per cent of the cases of Marshall<sup>77</sup> and Strömbeck.<sup>97</sup>

Schnitzler's<sup>173</sup> experience in 1 case was unique.

An appendectomy was performed on a patient, and there was relief of symptoms for eight years. Then abdominal symptoms again appeared, and a laparotomy was again undertaken in the erroneous and misleading belief that the appendix had not previously been removed. Swelling of the mesenteric glands was found at the second operation. The symptoms recurred subsequently. The obvious conclusion is that the appendix had nothing to do with the mesenteric lymphadenopathy.

If one combines the data in Schnitzler's case and the experience of Marshall<sup>77</sup> and that of Strömbeck<sup>97</sup> with the striking lack of pathologic change in the appendixes removed at operation in the presence of mesenteric adenitis, the total evidence seems to confirm the assumption that in the great majority of cases the appendix does not provide the causative agent for the swollen mesenteric glands, even though in rare instances it may do so.

*Small Intestine.*—Next in frequency and importance as the portal of entry for the cause of mesenteric lymphadenitis is the terminal part of the small intestine.

Guleke<sup>6</sup> and many other observers expressed the belief that the condition originates in the bowel. Various factors which might favor the passage of bacteria or their toxins through the wall of the bowel have been suggested. Distention, catarrhal inflammation, abrasions and other injuries of the mucous membrane, as well as lowered resistance of the surface epithelium of the bowel, have been mentioned by Bell,<sup>66</sup> Pribram,<sup>137</sup> Freeman<sup>2</sup> and Signorelli and Hosen.<sup>74</sup>

In this regard, the anatomic pattern according to which the local lymphadenoid apparatus and its connecting lymph channels are arranged is so striking in its similarity to that observed at the upper end of the

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173. Schnitzler, H.: Lymphangitis und Lymphadenitis mesenterialis, *Wien. klin. Wchnschr.* 46:134 (Feb. 3) 1933.

alimentary tract as to compel the assumption that the variety of diseases or lesions occurring in the latter must have counterparts in the terminal portion of the ileum and that, above all, the mechanism of the development of disease in two locations must be alike.

The anatomic pattern consists in either locality of (1) an aggregation of lymphadenoid tissue in the wall of the alimentary canal (in the neck, the adenoids and tonsils; in the terminal portion of the ileum, Peyer's patches and other solitary follicles) and (2) groups of lymph nodes anatomically related by position to these areas into which the normal drainage from these collections of lymphadenoid tissue flows (cervical glands in the neck; mesenteric glands in the abdomen). I have alluded to this anatomic arrangement many times and am much surprised that the importance of this has not received the attention which, to my mind, it richly deserves.

That the surface of the alimentary canal (oronasopharyngealbuccal mucosa of the terminal part of the ileum) is always a region full of potentiality for chemical, traumatic and, possibly, other forms of injury, leading to its constant possible role as a portal of entry for bacterial infection, is elementary knowledge. It remains but to compare the forms of bacterial infection and secondary lymphadenopathy in the two situations to show the importance of this knowledge in explaining the probably most common portal of entry and mechanism by which acute mesenteric adenitis of the type under discussion occurs.

Pediatricians will recognize as clinical facts that lymphadenopathy in the two situations occurs at similar ages and practically exclusively in young and growing children and adolescents and that in persons of these ages so-called "catarrhal" infections, in which lymphadenopathy is an important factor, are extremely common. In the neck these appear in two main forms. In the one a primary lesion is present in the oronasopharyngeal space and is easily recognized (teeth, mucous membrane, adenoids, tonsils, etc.). One recognizes without question that these primary lesions are portals of entry for the secondary infection in the associated cervical glands. In the other a primary lesion is not discoverable, although every clinician is certain that one is or has been present, and the forthcoming explanation includes the possibility that the lesion is hidden in some inaccessible place or has possibly undergone healing and evanescence at the time of examination. At present there is usually no discussion about this line of reasoning.

As to the abdomen, I dare say that no one will dispute the premise that if the mesenteric lymph nodes are enlarged the lesion is secondary to some preceding one in its immediate anatomic vicinity or has originated from a distant focus by the hematogenous route. In the former circumstances, under ordinary conditions, the area in which a potential primary lesion could develop is not accessible to examination, especially

visual or palpatory examination, even during an open laparotomy, and the opportunity for postmortem examination is, fortunately, almost nil. However, analogous knowledge and experience are available, as has been indicated previously for typhoid fever, nonspecific granuloma<sup>174</sup> of the terminal part of the ileum and for acute enterocolitis and ileocolitis.

The mechanism in each of these examples is characteristically alike, and there is no reason to assume that in cases of nonspecific simple adenitis a different mechanism would be employed. The conclusion, then, seems inevitable that a primary lesion must be present, even if it is not susceptible to discovery, in the adjacent and correlated part of the alimentary tract.

I wish to emphasize again the fact that in both segments of the alimentary tract—in the neck and in the abdomen—the primary lesion is located in an area in which there is an extraordinary abundance of lymphadenoid tissue. And in the abdominal conditions this is true in all of the examples cited in the foregoing sections as well as in cases of mesenteric adenitis. One takes it for granted that the progression of infection in the neck is from lymphadenoid collections to the cervical lymph nodes, and a similar line of reasoning is entirely applicable to the abdomen, where the Peyer's patches and the terminal portion of the ileum apparently assume a similar anatomicophysiologic purpose.

It seems difficult to avoid the assumption that the areas of the alimentary canal in which lymphadenoid tissue shows any abundance are particularly susceptible to these simple forms of nonspecific infection—nonspecific only because the specific cause is not known—and that these infections should take place during that period of life when so-called "catarrhal" infections in general are common. In previous years the abundance of attention given to the tonsils and adenoids has testified to their importance in these conditions, but, for very obvious reasons (lack of opportunity for observation, etc.), the importance of similar collections of lymphadenoid tissue in the small intestine has not received the attention which it deserves. This is what I should like to emphasize strongly.

This does not, however, restrict the area of origin of infection, either at the upper end of the alimentary canal or in the terminal portion of the ileum, entirely to the collections of lymphadenoid tissue. It is well known that in the mouth the buccal mucous membrane and the teeth can become points of entry for infection, and the same must undoubtedly be true for the reaches of the intestinal mucosa where lymphadenoid tissue is not present or is at a minimum. This does not destroy for

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174. Crohn, B. B.; Ginzburg, L., and Oppenheimer, G.: Regional Ileitis: Pathologic and Clinical Entity, *J. A. M. A.* **99**:1323 (Oct. 15) 1932. Rockey, E. W.: Thickening of Terminal Ileum with Mesenteric Adenitis in Children, *Northwest Med.* **32**:145 (April) 1933.

one moment the predominant role of the lymphadenoid tissue as probably the most frequent portal of entry for infection which later is transmitted to the cervical and/or the mesenteric glands. It also fortifies strongly the similarity of the anatomic and pathologic characteristics of the two areas.

*Hematogenous Infection.*—I do not think that Brennemann's<sup>32</sup> suggestion that pathogenic bacteria, which are permanently or temporarily present at the upper end of the alimentary canal (mouth and nasopharynx), may be transmitted by the blood stream and produce secondary inflammatory lesions in the intestine with subsequent involvement of the lymph glands or secondary lesions directly into the lymph glands without the interposition of the intestinal structure can be entirely dismissed. In my own experience and in that of others there have been any number of cases in which a frank infection of the nasopharynx (acute follicular tonsillitis, for instance) has been followed by an acute embolic form of gangrenous appendicitis, and sometimes the appendical lesion has flared up and dominated the clinical picture even before the nasopharyngeal lesion has healed. I am sure that this experience can be multiplied a thousandfold in the experience of other surgeons. I think myself that cases in which simple mesenteric adenitis occurs in this way are in the minority.

*Lymphatic Absorption.*—One of the hypotheses about mesenteric lymphadenitis seems to result from some general idea that the lymphatic system exists as a homogenous unit for the entire body rather than as a collection of separate units each for a physiologically demarcated part. In 1903, MacFadyen and MacConkey<sup>175</sup> referred to the unanimity of the lymphatic system with special reference to the faucial tonsils, the adenoids and the mesenteric lymph nodes. Some sort of clinical corroboration for this exists in an observation which has been made a number of times in the last few years, namely, that in some of the cases of acute involvement an infection of the upper respiratory tract either precedes or occurs simultaneously with the abdominal manifestations.

A characteristic experience was reported by Noya Benitez.<sup>176</sup> In a series of 9 children he obtained a history of an attack of cold and cough for a few days, preceding the onset of abdominal pain with nausea, vomiting, fever and tenderness and spasm in the right lower quadrant of the abdomen. There was a history of similar recurrent and subacute attacks in the past. Leukocytosis was always present during the attack.

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175. MacFadyen, A., and MacConkey, A.: An Experimental Examination of Mesenteric Glands, Tonsils, and Adenoids, *Brit. M. J.* 2:129, 1903.

176. Noya Benitez, J.: Acute Mesenteric Lymphadenitis, *Bol. Asoc. méd. de Puerto Rico* 32:8 (Jan.) 1940.

*Pharyngeal Infection.*—The general term pharyngeal infection is used to include "that whole group of nonspecific, sporadic, endemic, epidemic, pandemic, febrile infections that have their primary locus in the nose and throat and are variously called tonsillitis, pharyngitis, nasopharyngitis, sore throat, cold, streptococcus throats, rhinitis, laryngitis, bronchitis, upper respiratory tract infection, angina, glandular fever, grip, or influenza" (Brennemann<sup>32</sup>).

Pediatricians are well acquainted with the fact that during such infections abdominal symptoms—pain, nausea and vomiting—with fever and other signs of a bacterial infection are common. Conversely speaking, observers have noted that frequently abdominal symptoms of which mesenteric adenitis has been demonstrated to be an accompaniment or sequel are preceded by or even accompanied with some such "throat infection." As most of the patients are children in whom infections of this kind are notoriously common, such a history may indicate a mere coincidence. The excessive frequency of this progression seems to invite the assumption, however, that a biologic connection of some kind exists. Transmission to the abdominal glands by a hematogenous infection is emphasized by some, but there is also the possibility, which is stressed by others, that the organisms are swallowed and passed along to the appropriate segment of the intestine, from which absorption occurs into the mesenteric glands. Possibly both methods of transmission occur individually or simultaneously; when there seems to be simultaneous involvement of the two regions, the hematogenous mechanism seems to be the correct answer; when the abdominal manifestations follow the "throat infection" by an appreciable interval, the second explanation seems more probable.

In the hematogenous conditions the presumption is that the organisms enter the circulation through the oropharynx, are distributed throughout the body and form a metastatic focus in the abdominal glands. In the dysenteric conditions, Felsen<sup>76</sup> has reported that this can be reproduced in animals not only with the bacteria but also with their toxins. It seems a little difficult to understand, however, why no regional group of glands besides the abdominal group are similarly affected.

In the second group—in which the organisms are said to be swallowed—one might presume to postulate, by analogy with the cervical conditions, that the organisms enter through some break in the mucosa of the ileum, which, under the circumstances, is not susceptible to investigation or not demonstrable even if investigation were possible. The secondary blockage in the appropriate lymph nodes creates the clinical concept of mesenteric adenitis. That such bacterial transit without a demonstrable lesion in the mucosa is possible is supported by

the knowledge that bacteria are probably routinely absorbed together with the products of digestion and are eliminated or blocked in the mesenteric nodes.

A curious observation in connection with this is that of Felsen,<sup>76</sup> who described a similar form of infection of the upper respiratory tract with mesenteric adenitis which he has occasionally noted to precede an attack of the Sonne-Duval type of bacillary dysentery in children. And Alvarez,<sup>37</sup> Barga<sup>177</sup> and Barron<sup>178</sup> said specifically that attacks of chronic ulcerative colitis and recurrence of symptoms often follow acute infections of the respiratory tract, such as bronchitis, tonsillitis, rhinitis, influenza or pneumonia.

Whether in these cases it is, perhaps, a general toxemia that brings about the mesenteric lymphadenopathy or whether the cause of the infection is absorbed into the blood stream and is then simultaneously distributed into all parts of the lymphatic system, for which it has some sort of predilection, is still to be settled.

#### IMPORTANCE OF LYMPHADENOID TISSUE

The important role played by the lymphadenoid tissue of the alimentary canal is correctly appreciated only when one realizes the great frequency with which it becomes involved in the various diseases known to clinical medicine. The tangible knowledge indicates an astonishingly large incidence of involvement of the mesenteric glands in typhoid and paratyphoid fever, in the various forms of bacteremia, in status lymphaticus, in tuberculosis, rarely in syphilis and actinomycosis, more commonly in the various blood dyscrasias, in a case of agranulocytosis reported by Felsen<sup>76</sup> and in the various forms of colitis, enteritis and dysentery. This list does not include the various forms of malignant tumor and such borderline lesions as Hodgkin's disease. As has been indicated, for some of these, such as typhoid fever, the mechanism of development and of the transit of the infection is well known. The newer anatomic knowledge of colitis and dysentery indicates a fairly close approximation to the latter.

In all forms of diarrheal disease in infants and children (infantile diarrhea, cholera infantum, acute ileocolitis, summer diarrhea, etc.) the process seems to center in or to show a predilection for the vicinity and substance of the intestinal lymphadenoid nodules, being especially marked in Peyer's patches. Apparently all of these conditions begin as surface infections and reach down into the substance of the intestinal wall as

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177. Barga, J. A.: Etiology of Chronic Ulcerative Colitis, J. A. M. A. **83**: 332 (Aug. 2) 1924.

178. Barron, M. E.: Simple Non-Specific Ulcer of the Colon, Arch. Surg. **17**:355 (Sept.) 1928.



the pathologic process proceeds. The spread into the wall occurs along the lymph channels into collections of lymphadenoid tissue (solitary follicles; Peyer's patches). Wherever in the various publications (Holt;<sup>179</sup> Felsen<sup>76</sup>) particular attention has been paid to this element and the findings recorded, it is astonishing to see how often specific mention is made of the localization about, and the involvement of, Peyer's patches. In this regard the differentiation between the small and the large intestine is merely a quantitative one and depends on the distribution of solitary and aggregated collections of lymphadenoid tissue (solitary follicles; Peyer's patches). In the small intestine it is common to find the lesion localized for the most part and/or limited to the lower part of the ileum, where the lymphadenoid tissue abounds to such a large extent in the intestinal wall. The spread into and the involvement of the adjacent tissues of the intestinal wall become visible only with the prolongation of the illness and its anatomic development.

So-called catarrhal infections are commonly associated regionally with the upper reaches of the alimentary canal and have been previously referred to under the general heading of pharyngeal infections. For the most part these occur anatomically in relation to the lymphadenoid apparatus of the tonsils and adenoids and their secondary involvements in the cervical glands. They are commonly said to be "surface" infections. Whether such "catarrhal" infections can occur deep in the ileum and originate in and about Peyer's patches is apparently beyond the present available powers of demonstration, but certainly in cases of simple mesenteric adenitis without other demonstrable lesions there are symptomatic and anatomic manifestations identical to those of similar lesions that originate in the oropharynx. The interplay of "throat" infection with abdominal symptoms as indicated in this communication is more than a mere coincidence and is remarkable.

#### RÉSUMÉ AND COMMENT

I have gone far afield to show the protean character of the pathologic conditions with which general and/or mesenteric lymphadenopathy can occur in clinical medical practice. To be sure, lymphadenopathies of one kind or another in other areas of the body are well known to physicians, in contradistinction to the mesenteric area, where their secluded position has until recently served to prevent sufficient examination and study. It appears that the correspondence between the abdominal field and other regions of the body is identical and that some of the lymphadenopathies in the mesenteric area can be of maximum grade; thence the gradations and severities vary all the way down to the great majority

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179. Holt, L. E.: *The Diseases of Infancy and Childhood*, New York, D. Appleton and Company, 1906.

of the instances of those apparently simple and more benign cases of mesenteric adenitis which are especially under discussion.

A number of concepts have resulted from this factual review:

1. A very important common denominator of all of this aggregation of facts—namely, the age factor. It is apparent that all of the conditions hereinbefore reviewed with which general and/or mesenteric lymphadenopathy is associated occur in the period beginning with childhood and extending with less frequency up to the adolescent period. It appears from this that during this period of life the lymphatic apparatus of the human being is under continual and variegated stress and is most apt to undergo pathologic changes.

2. The great frequency with which streptococci are associated with the various forms of so-called nonspecific lymphadenopathy and with the various clinically differentiated illnesses referred to. To be sure, other organisms, staphylococci, diplococci, melitensis organisms and others are named even in conditions not specifically defined as clinical diseases, such as typhoid fever. But the predominating organism is the streptococcus.

An interesting fact about all of these conditions also is the frequency with which streptococci of various strains can be obtained in cultures from the oropharynx. The fact that streptococci find a "normal" habitat in the tonsils, in the pharyngeal mucosa and about the teeth does not invalidate an assumed pathologic connection between the organisms, an originating oropharyngeal infection, secondary adenitis in the neck and/or an abdominal lymphadenopathy, if no other organisms can be recovered and if no other specific form of infection, concerning the cause of which one has complete knowledge, is present. This is especially so in that large, vaguely defined group of diseases, customarily called, for want of a better name, "rheumatic." The presence of these streptococci seems to be of some etiologic importance when applied to the mesenteric gland enlargements, as streptococci of various kinds have been by far the most frequent organisms in cultures of material taken from the abdominal lymph nodes.

3. The great facility with which generalized and/or mesenteric lymphadenopathies are associated with many apparently widely differing diseases, indicating the great tendency for lymphatic absorption of these diseases during this period of life.

4. The great frequency with which these diverse forms of disease during this period of life are ushered in with gastrointestinal symptoms, with "throat" conditions or with both, indicating the extreme importance of the alimentary canal as a whole or in part as a portal of entry for the causative agent.

The opportunities for absorption of any causative agent are remarkable, including that associated with the normal digestive functions and that predicated on the occurrence of local points of injury. The passage of any provocative causative agent from the oral cavity to the terminal portion of the ileum is a constant occurrence, and it is most remarkable that these forms of infection do not occur with greater frequency.

It is practically impossible to obtain an accurate visualization of the general and ordinary condition of the enormous surface of the mucous membrane of the intestinal tract, especially of the jejunoileum. It seems highly probable, nevertheless, that more frequently than one ordinarily imagines there is some inflammation of this membrane (i. e., enteritis). There is every reason to believe that such inflammation can be responsible for many hitherto not sufficiently explained abdominal symptoms—acute and chronic upsets in digestion, cyclic vomiting, etc.—which are now thought to be “functional” in origin; for many forms of diarrhea for which, at present, no adequate cause can be found, and for some of the other transient disturbances in the functions of the stomach and bowel which commonly accompany “colds,” “throat infections” or other generalized infections. Accurate correlation and integration of these symptoms with the little and infrequently available knowledge obtained during postmortem examination are difficult. Common bacteriologic causes for such transient and often unrecognized forms of enteritis may be the organisms and/or their toxins of the dysentery, enteritides and colon groups of bacteria, as well as staphylococci and streptococci. The studies of Childrey, Alvarez and Mann<sup>180</sup> indicate that the digestive upsets that follow the eating of too much food or of indigestible food may well be due to injury wrought in this way to the absorptive power of the mucous membrane of the bowel.

I am more and more impressed by the frequency with which causative agents of disease attack and enter the body through the upper end of the alimentary canal (oronasopharynx). There is a good deal of evidence that the association of infection at the beginning of the alimentary canal (oropharyngeal cavity) with the abdominal manifestations centering in the general region of the terminal portion of the ileum is no mere coincidence. Corroboration of this has been obtained both in experimental work (Poynton and Paine;<sup>181</sup> Adrain<sup>182</sup>) and in clinical

180. Childrey, H. W.; Alvarez, W. C., and Mann, F. C.: Digestion: Efficiency with Various Foods and Under Various Conditions, *Arch. Int. Med.* **46**:361-374 (Sept.) 1930.

181. Poynton, F. J., and Paine, A.: *Researches on Rheumatism*, New York, The Macmillan Company, 1914, pp. 374-377; *A Further Contribution to the Study of the Etiology of Appendicitis as a Result of Blood Infection, with Particular Reference to the Tonsils as a Primary Seat of Infection*, *Lancet* **2**:439 (Aug. 17) 1912.

182. Adrian, cited by Poynton and Paine.<sup>181</sup>

practice. Similarly, in the literature reference has been made to the connection of appendicitis and an originating oropharyngeal infection.

At the upper end of the alimentary canal there are local and regional means (cervical glands) in abundance for neutralizing such absorbed infection, but not rarely this mechanism breaks down. Then the oronasopharynx acts as a point of general distribution throughout the body, through the hematogenous route, through the lymphatic apparatus and by swallowing and passage along the alimentary tract. It is possible, therefore, for secondary effects to occur in any one of three ways, and even when other symptom complexes appear enlargements of the lymph glands can occur in other parts of the body (mesenteric lymphadenopathy) apparently unrelated to the symptom complex present. When abdominal lymphadenopathy occurs, then, other than local causes must be considered. This explains the rare local effect of acute appendicitis or the more common local effect of enteritis in causing mesenteric adenitis, and the frequent occurrence of abdominal symptoms as one of the general distribution effects with which many conditions are ushered in and of which the "rheumatic group" is a good example.

I have been struck by the observation that a great many of the collateral conditions previously discussed, especially those usually associated loosely in the "rheumatic" group, are tied up in some way or other with infections beginning at the upper end of the alimentary canal, in the oropharynx, and with enlargement of the mesenteric nodes. Many of these are frequently ushered in with abdominal manifestations, sometimes with fever and sometimes without; sometimes with vomiting and occasionally with diarrhea; sometimes in isolated cases; at other times in more or less epidemic form, and sometimes as interepidemic, influenza-like infections. Formerly some of these abdominal manifestations were referred to as "cyclic vomiting" or as "acidosis." While all of this may and probably does indicate a certain amount of looseness of thought among observers, the one thing that stands out is the fact that a good many of these conditions are in some way associated at the onset with oropharyngeal infections and that in many of them abdominal lymphadenopathy is present.

I am also struck by the observation that in some of the exanthems the disease is ushered in with so-called "catarrhal" symptoms of pharyngeal infection. In many of these there are also initial gastrointestinal symptoms. In some of the exanthems, at least, one knows that the rash spreads downward and is present on the surface of the alimentary canal, which biologically and physiologically is also an "external" skin of the body. In some of the exanthems, as has been pointed out, it is known that lymph gland enlargements occur throughout the body, and more often than is known these occur also in the abdomen.

Two conclusions seem to be unavoidable: (1) that the spread is by the hematogenous route and (2) that the enlargement of the abdominal lymph glands is related to the hematogenous infection and/or to the presence of the exanthem.

I am also struck with the importance of an allergic mechanism in many of the previously mentioned conditions. The rapid and abundant distribution of an exanthematic rash is probably based on an allergic distribution. In the visceral crises the edematous areas in the intestinal tract show remarkable similarities to external forms of angioneurotic edema and are undoubtedly indicative of a similar mechanism. Various forms of purpura commonly accompany the visceral crises. In the hyperacute, fatal form of purpura there is indication of an overpowering biologic mechanism, and no other branch of medicine comes so quickly to one's mind as that pertaining to allergic phenomena. Most probably the allergic antigen in any case is a bacterial product. Some of the phenomena remind one of histamine poisoning, and histamine-like bodies are found commonly in the intestinal tract. This should be compared with the section on allergy in the previous part of this paper and with Wise's case.

#### CONCLUSIONS

General abdominal lymphadenopathies are similar to lymphadenopathies in other regional areas. In the abdomen many of them are parts of a distinct symptom complex, such as typhoid fever or dysentery. Others are related to loosely gathered clinical entities known collectively as the "rheumatic" group of diseases. Still others are related to various conditions associated with generalized cutaneous manifestations, including some of the exanthems. A large group seems to be related to a preceding "catarrhal" or "throat" infection, and this seems to have some relation to forms of glandular fever, infectious mononucleosis and what is clinically known as abdominal grip. Finally, there is a type in which the lymphadenopathy cannot be clinically connected with any demonstrable preceding or accompanying lesion. Because of this fact the last-mentioned type has been considered still undemarcated and undifferentiated and is called, for want of a better term, nonspecific mesenteric adenitis.

Not always is the causative agent demonstrable. In only a minority of the latter cases can bacteria be demonstrated in the glands, and the predominating organism is some strain of streptococcus. Occasionally other, bizarre organisms, such as *B. melitensis*, can be cultured. An unidentified virus has also been suggested as the causative agent, but the correlation of this virus with that which may cause poliomyelitis has not been proved. No relation with lymphogranuloma venereum can be demonstrated by the Frei test. And, although various parasites have

been found to occur in the intra-abdominal lymph nodes, a causal relation cannot be established between them and nonspecific mesenteric adenitis.

The portal of entry for the causative agent for nonspecific mesenteric adenitis is only on rare occasions the appendix; and this can happen only because of some anatomic abnormality of the lymphatic drainage pathways of the appendix. More commonly the portal of entry seems to be related to "catarrhal" or "throat" infections, and least commonly the condition is a manifestation of a hematogenous mechanism or (more frequently) of a causative agent swallowed from the oropharynx and passed along to the terminal portion of the ileum, from which local absorption occurs. Most often of all the nonspecific mesenteric adenitis is a local effect of absorption from some local nondemonstrable lesion in the ileal segment of the alimentary canal; it can be safely assumed that this includes various forms of transient enteritis and other surface infections, various gross and microscopic injuries and other forms of physical and chemical trauma.

In this most common mechanism the similarity to the ordinarily observed phenomena of cervical adenitis is absolute. In either case local injuries and infections permit the passage of the causative agent to the appropriate lymph nodes. The mechanism is based on an exact duplication in the two positions of the anatomic arrangement of the local lymphadenoid tissue in the wall of the alimentary canal and of the corresponding lymph nodes. And the heaping up of extraordinary collections of lymphadenoid tissue in the wall of the alimentary canal at both of these locations is remarkable and seems important from an etiologic and a mechanistic point of view.

As in many cases abdominal lymphadenopathy is part and parcel of some larger definite clinical entity, treatment must follow along the lines known by experience to be correct and adequate for the original disease. In the presence of nonspecific mesenteric adenitis and in the absence of any suppuration or other complication, none but conservative treatment would be indicated if one could so perfectly diagnose the condition that the fear of undiscovered acute appendicitis or other surgical emergency could be definitely eliminated. Unfortunately, this is not possible in clinical practice at the present writing, and abdominal explorations are more or less frequently necessary in order to establish the true nature of the intra-abdominal condition.

# EXPERIMENTAL BILE PANCREATITIS

## WITH SPECIAL REFERENCE TO RECOVERY AND TO THE TOXICITY OF THE HEMORRHAGIC EXUDATE

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Claude Bernard in 1856 first produced experimental pancreatitis by the injection of bile and olive oil into the pancreatic ducts of animals. Opie<sup>1</sup> first associated cholelithiasis with pancreatitis and suggested that the impaction of a gallstone at the "ampulla" produced a common channel and pancreatitis from the entrance of bile into the pancreatic duct. Archibald<sup>2</sup> expressed the belief that uninfected bile would produce only acute edema of the pancreas, which usually subsided within a relatively short time. Rich<sup>3</sup> recently suggested that metaplasia of the duct epithelium may produce obstruction with subsequent rupture of the duct and that the liberated trypsinogen is activated by contact with the tissues, with the resultant development of the acute pancreatitis. Some physiologists believe that the pancreas can at times secrete activated trypsin.

Dragstedt, Haymond and Ellis<sup>4</sup> expressed the opinion that acute pancreatitis is produced by direct chemical action of the bile salts and not by the activation of the trypsinogen. Wangensteen, Leven and Manson<sup>5</sup> stated the opinion that the cause of acute pancreatic necrosis is to be found in a combination of factors, any one of which, operating alone, would be inadequate to produce the disease. They gave especial consideration to the activation of trypsinogen, with production of pancreatic necrosis.

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From the Department of Surgery, the University of Illinois College of Medicine.

Submitted in partial fulfillment of requirements related to the degree of Master of Science in Surgery.

1. Opie, E. L.: Etiology of Acute Hemorrhagic Pancreatitis, *Bull. Johns Hopkins Hosp.* **12**:182, 1901.

2. Archibald, E.: Acute Edema of Pancreas, *Ann. Surg.* **90**:803, 1929.

3. Rich, A. R., and Duff, G. L.: Experimental and Pathological Studies on Pathogenesis of Acute Hemorrhagic Pancreatitis, *Bull. Johns Hopkins Hosp.* **58**: 212, 1936.

4. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Pathogenesis of Acute Pancreatitis, *Arch. Surg.* **28**:232 (Feb.) 1934.

5. Wangensteen, O. H.; Leven, N. L., and Manson, M. H.: Acute Pancreatitis, *Arch. Surg.* **23**:47 (July) 1931.

The information regarding the power of the pancreas to regenerate was scanty until Bensley's<sup>6</sup> important contribution appeared, in 1911. To a great extent this paucity of information relative to regeneration was due to the lack of proper staining technic. Bizzozzer and Vassole (1887) observed mitoses in duct and acinar cells in the pancreas of adult mammals. Ssobolew (1902), in his classic work on results of ligation of the pancreatic duct, showed that when the permeability of the duct was reestablished the gland regenerated. Bensley expressed the belief that under appropriate conditions the pancreas is able to regenerate to a remarkable degree and also that the regenerative emphasis seems to lie on the islet side as long as the duct remains closed but shifts to the acinous tissue as soon as the communication with the bowel is reestablished. Grauer<sup>7</sup> concluded that the rabbit pancreas is a highly plastic organ, capable of undergoing a change of structure with astonishing rapidity, and that the regeneration of the acini proceeds much more rapidly if the patency of the duct is intact. Bensley and Grauer jointly stated that duct epithelium is the source of all growth and repair in the pancreas.

Parker,<sup>8</sup> in 100 of 400 routine autopsies, observed mitotic figures in the acinar cells of the pancreas. Ukai<sup>9</sup> stated the belief that there is marked proliferation of the acini in the early stages after transplantation of pancreas. Shaw and Latimer<sup>10</sup> stated that they observed definite regeneration of glandular tissue from transplanted duct epithelium. Brocq,<sup>11</sup> expressing disagreement with most authors, found no evidence whatsoever of acinar regeneration. Jorns<sup>12</sup> found sustained acinar regeneration only at the periphery of transplants in free grafts of degenerated pancreas after ligation of the ducts. Maximow<sup>13</sup> stated the opinion that the adult pancreas has undifferentiated cells in the epithelium of the smaller tubules with sufficient regenerative power to give rise to new parenchymal tissue.

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6. Bensley, R. R.: Studies on Guinea Pig Pancreas, *Am. J. Anat.* **12**:297, 1911.

7. Grauer, T. P.: Regeneration in Pancreas of Rabbit, *Am. J. Anat.* **38**:233, 1926.

8. Parker, E., Jr.: Toxic Necrosis and Regeneration of Acinar Cells of the Pancreas, *J. M. Research* **40**:471, 1919.

9. Ukai, S.: Study of the Transplanted Pancreas, *Zentralorgan f. d. ges. Chir.* **31**:705, 1925.

10. Shaw, J. W., and Latimer, E. O.: Regeneration of Pancreatic Tissue from Transplanted Duct of the Dog, *Am. J. Physiol.* **76**:49, 1926.

11. Brocq, P.: *Les pancréatites aiguës chirurgicales*, Paris, Masson & Cie, 1926.

12. Jorns, G.: Concerning the Regeneration of the Pancreatic Duct in Free Transplants of the Pancreas, *Beitr. z. klin. Chir.* **138**:682, 1927.

13. Maximow, A. A., and Bloom, W.: *Textbook of Histology*, Philadelphia, W. B. Saunders Company, 1930.



Elman,<sup>14</sup> in a recent article, concluded that acute edema of the pancreas represents a distinct clinical and pathologic entity and not merely an early stage of pancreatic necrosis, as was brought out by Zoepffel.<sup>15</sup> Some observers believe that fat necrosis can exist without the slightest involvement of the pancreatic parenchyma. However, most workers contend that fat necrosis is secondary to acute pancreatitis. Guibal<sup>16</sup> expressed the belief that venous thrombosis and thrombophlebitis are essential in the production of pancreatic necrosis and fat necrosis.

#### EXPERIMENTAL TECHNIC

In the following experiments pancreatitis was produced by the introduction of 2 to 6 cc. of bile (proved sterile by culture) into the accessory duct of the dog's pancreas. The bile in each instance was obtained from the gallbladder of the animal used. In all, 40 animals were used. A maximum of 10 cc. of bile was injected into 1 dog. None of the dogs in this series had been fed for the previous twenty-four hours. Most of the animals weighed about 10 Kg. A ligature was not placed on the duct after the injection, as it was desired to maintain its patency. The bile was introduced slowly in some animals and rapidly in others; however, the rapidity of injection seemed to have no effect on the type of pathologic change produced, the total amount of bile used being the only consistently effective factor in the type of pancreatitis produced. The severity of the pancreatitis seemed dependent to a great extent on the concentration of the bile injected. In the few instances in which one could note a distinct difference in concentration of the bile introduced, the animals into whose ducts the dark, presumably concentrated bile was injected were more apt to have a severe type of pancreatitis. This conforms to the results of Archibald's experiments.<sup>17</sup> The color of the pancreas changed to yellow-brown during the injection. Within two or three minutes the entire pancreas had been transformed by the characteristic "glassy edema" described by Zoepffel.<sup>15</sup> A biopsy specimen of the pancreas taken at this stage showed, grossly, the pancreatic lobules separated by gray edematous tissue, producing enlargement to about twice the normal size. Most of the animals were reoperated on within the first twenty-four to forty-eight hours after injection, biopsy specimens of the pancreas and liver being taken for microscopic section. The specimens were taken through the areas containing the most marked changes. The dogs that survived were killed at varying times postoperatively in order to obtain observations at weekly intervals after injection into the duct (for eight weeks). Although edema or the more severe types of pancreatitis could be produced in every animal, it seems probable from the results that the amount of bile injected or the concentration of the bile salts therein greatly influences the severity of the pancreatitis, as was noted by Archibald.<sup>17</sup>

14. Elman, R.: *Acute Interstitial Pancreatitis*, Surg., Gynec. & Obst. **57**:291, 1933.

15. Zoepffel, H.: *Acute Pancreatic Edema*, Deutsche Ztschr. f. Chir. **175**:301, 1922.

16. Guibal, A., and others: *Acute Necrosis of the Pancreas*, Ann. d'anat. path. **15**:249, 1938.

17. Archibald, E.: *Experimental Production of Pancreatitis in Animals*, Surg., Gynec. & Obst. **28**:529, 1919.

Animals which received  $1\frac{1}{2}$  grains (0.09 Gm.) of morphine sulfate immediately after the operation and those in which the omentum was wrapped around the pancreas after injection seemed to fare slightly better than did those for which these procedures were not used. The clinical condition on the first postoperative day was regarded as good for 14 animals, fair for 13 and poor for 13. Those classified as in good condition were up and about, barking and able to eat the usual daily food. Those considered in fair condition were usually up, ate some food, responded only occasionally and appeared rather listless. Those judged to be in poor condition were completely prostrated, cold and shivering, vomiting and absolutely unresponsive. All the animals that appeared prostrated on the first day after injection died within the first forty-eight hours. The animals received no postoperative therapy except the morphine mentioned previously.

### RESULTS

The gross findings on reopening the peritoneal cavity were as follows: In a majority of cases diffuse fat necrosis, involving especially the upper abdominal structures, was noted. Fat necrosis occurred in 33 animals, the pancreatitis in 8 being of the edematous type and in the remainder of the hemorrhagic and necrotic type. The necrosis of the fat varied from spots here and there to massive involvement of almost the entire omentum, mesentery, etc. A hemorrhagic exudate was found in the peritoneal cavity in 30 animals and varied in amount from 25 to over 100 cc. The hemorrhagic exudate was present in 8 animals with acute edema of the pancreas. Acute edema or the more severe hemorrhagic and necrotic type of pancreatitis was produced in every dog, conforming in general to the experience of others. There were 15 instances of acute edema with no other parenchymatous pathologic changes. The remaining 25 dogs had mild to moderately severe hemorrhagic and necrotic pancreatitis. There were 9 animals with gross pancreatic necrosis and 4 with severe necrosis. The dog into which 10 cc. of sterile bile had been injected had the most severe necrosis of the gland and died in less than eight hours after the injection. Its pancreas was almost completely black except for a couple of small areas in the proximal third. The pancreas was enlarged to at least twice the normal size in all cases, regardless of the type of lesion encountered. No gross abscesses were found except occasionally around the pancreatic duct (point of injection). The wall of the duodenum was frequently hemorrhagic and thickened. Grossly the liver appeared little changed except for slight swelling and congestion, its surface being dull red-gray. The pancreas in the acute edematous condition appeared fairly normal except for its enlargement and its yellow-brown tint. To palpation the edematous pancreas felt tense, thickened and rubbery. In some instances the gland contained hemorrhagic areas averaging 1 cm. in diameter. Occasionally there would be small subcapsular hemorrhages, which did not appear to extend into the parenchyma.

A hematoxylin and eosin stain was used for all microscopic sections. The microscopic lesions in the pancreas were extensive. At first glance one was impressed by the massive edema in all the types of pancreatitis encountered. This edema was both interlobular and interacinar. The most striking feature noted was the patchy nature of the hemorrhagic and necrotic areas. In general, when there was not mass necrosis of the entire lobule or lobules most of the changes were located centrally in the lobule. The layers of acini surrounding the periphery of the lobule, although they showed some atrophy, were consistently less injured than the central portion, as has been noted by some authors. The completely necrotic

areas of parenchyma varied from a few cells to many acini, but only occasionally was the entire lobule involved. The acini differed from apparently normal cells in the acute edematous type through all the stages of degeneration in the hemorrhagic and necrotic type. The cellular changes to be studied in this report represent those found in acini which were only partially destroyed but retained their nuclear membrane intact. These cells had their membrane partially disrupted, with some loss of cytoplasm. The remaining cytoplasm appeared swollen

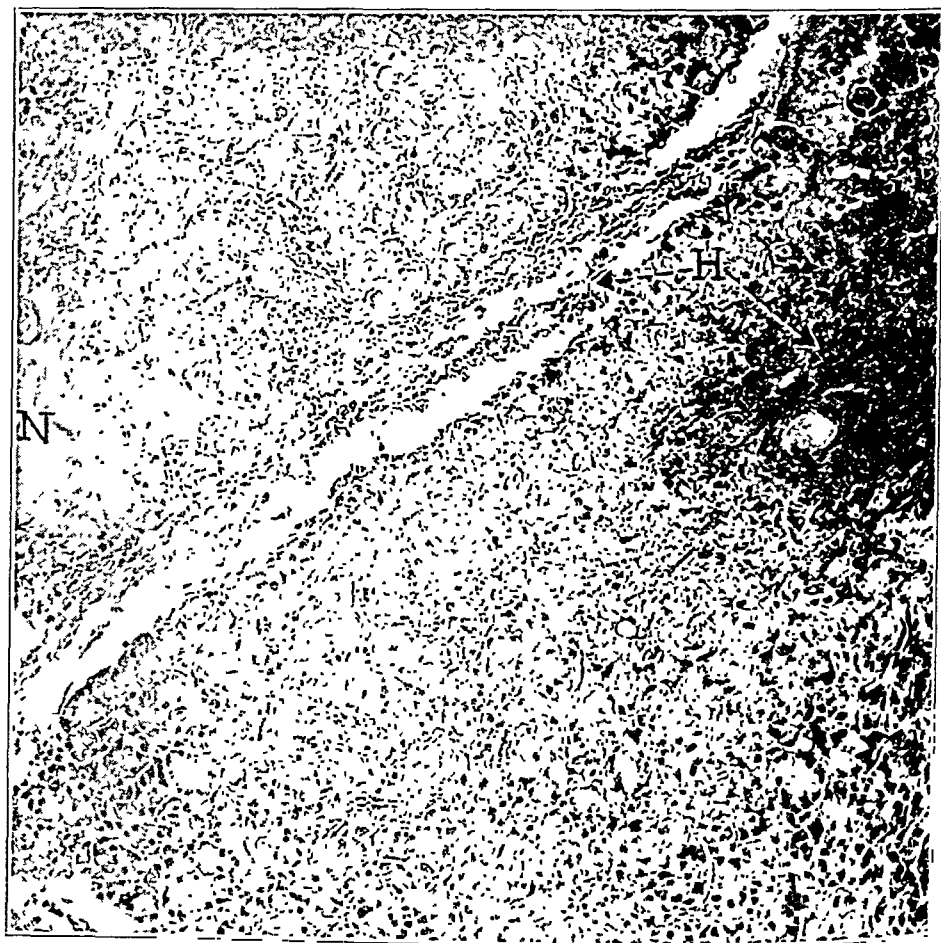


Fig. 1.—Photomicrograph of the pancreas, showing the patchy nature of the hemorrhage and necrosis (in experimental pancreatitis produced forty-eight hours previously), with fairly normal acinar cells adjacent. *H* represents areas of hemorrhage; *N*, an area of complete necrosis. The dog recovered symptomatically and was killed several weeks later.

with vacuoles throughout. The nuclear membrane in these partially injured cells was still intact, though the nuclei took the stain poorly in some and were pyknotic in others. Recovery of cells is possible if the nuclear membrane remains intact and karyolysis does not occur. The islet cells showed moderate cellular changes with slight disruption of the cytoplasm and some loss of the nuclear stain. The

pancreatic ducts were also markedly involved in the pathologic process. In general, it was noted that the larger ducts were less involved than the smaller ducts. The destructive process was microscopically more pronounced in the centroacinar cells and the epithelium lining the smaller tubules. This is probably to be explained by a thinner cell membrane and a more recent maturity. In some instances a cross section of a larger duct showed an almost normal lining epithelium, while inside the lumen were many red blood cells, debris, degenerated epithelial casts of the smaller

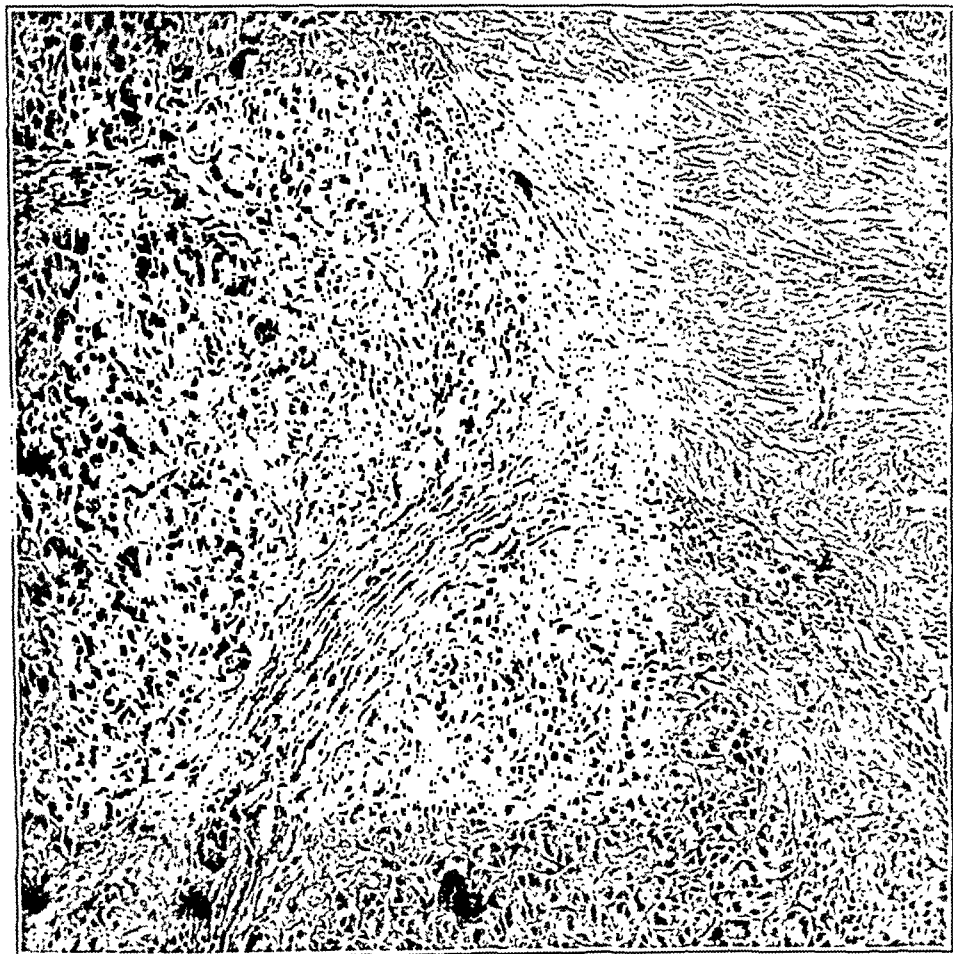


Fig. 2.—Photomicrograph of the pancreas (biopsy specimen obtained by operation) two weeks after production of the pancreatitis, showing disarrangement of the acini. These areas undoubtedly represent tissue the cells in which were partially damaged when the acute pancreatitis was produced. It is probable that a few cells were completely destroyed, which explains the misshapen acini. The area of dense fibrosis on the right was no doubt an area of complete necrosis.

tubules and fragments of the same. Cross section of the smaller tubules just adjacent showed slight disruption of the cytoplasm with loss of nuclear stain to complete absence of the lining epithelium. In animals with more severe pancreatitis even the larger ducts were involved, with complete loss of lining epithelium

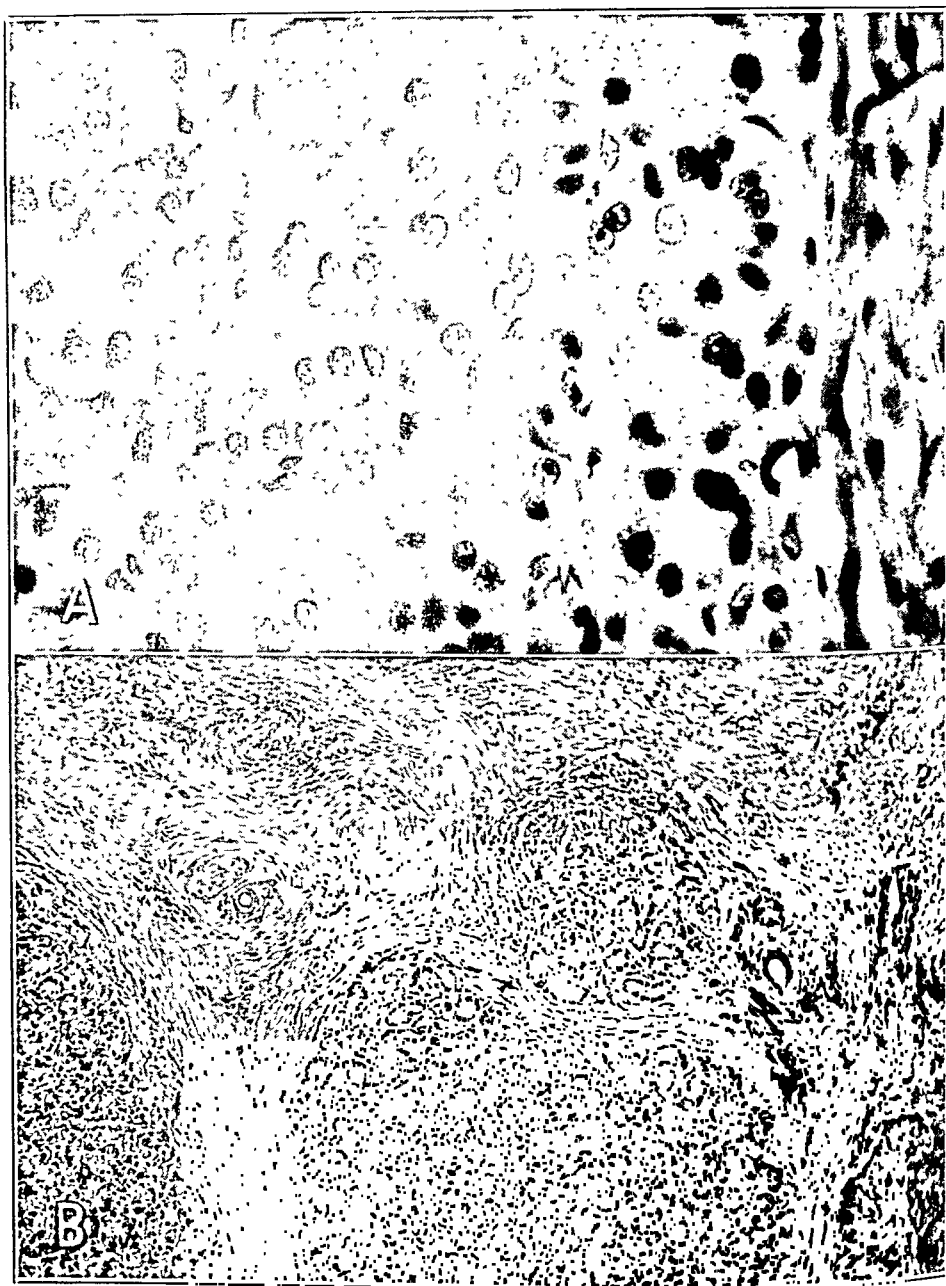


Fig. 3.—*A*, photomicrograph (high power) of the pancreas shown in figure 2, depicting the misshapen acini, which are apparently recovering histologically. A slight amount of interacinar fibrosis is noted. *B*, photomicrograph of the pancreas thirty days after injection of bile into the duct, showing disarranged acinar and lobular architecture but a more definite outline to the acini and better staining of the nuclei than were noted in the earlier biopsy specimen as depicted in figure 2.

and massive hemorrhage into the wall and lumen of the duct. The interlobular edema appeared to represent about one third to one half of the width of the lobule; the interacinar edema, about one quarter of the diameter of the acini. Young fibroblasts forming a fibrillar network were noted in the interacinar and interlobular spaces as early as the end of the first twenty-four hours. Polymorphonuclear cells and lymphocytes were seen throughout, and occasionally microscopic focal abscesses were demonstrated. In some sections there were marked interlobular hemorrhages. Microscopically, the biopsy specimen taken immediately after the injection of 10 cc. of sterile bile showed only edema, while the specimen taken shortly before death (six hours after injection) from the same animal presented occasional areas of hemorrhage with mass necrosis of entire lobules. Death occurred a few hours later.

The changes in the pancreas during its recovery, as observed microscopically, were as follows: The new fibroblastic tissue had proliferated so rapidly that by the end of the first week the interlobular spaces were fairly solidly filled with young fibrous tissue. The interacinar spaces surrounding the disrupted acinar cells that still had their nuclear membrane intact were also filled with young fibrous tissue. This process advanced so rapidly that the acinar cells attempting to recover their normal shape were molded, so to speak, in a new shape. This eventually gave rise to a bizarre-looking lobule with disarrangement of the acini, as seen in figure 2, fifteen days after injection. A higher power study of this same section (fig. 3 *A*) demonstrated the interacinar fibrosis, the misshapen acini and the apparent partial recovery of the cells and nuclei. This was demonstrated by the fact that the cytoplasm appeared to have a cell membrane; the vacuoles were infrequent, and there was little, if any, swelling of the cytoplasm. The nuclei took the stain well, and pyknosis was fairly rare. The ducts in some showed signs of what seemed to be proliferation of the epithelial lining (fig. 6).

This showed a large duct with complete loss of lining epithelium. In the wall were noted irregular nests of epithelial cells in tubular formation, with no definite arrangement. The number of cells in these nests varied from several up to twenty or more. The cells were large, with a clear cytoplasm and large vesicular nuclei, there being at least ten or fifteen groups of the nests just described. These groups of cells were regarded as proliferating duct epithelium. By the end of the first four weeks the dense fibrosis had almost entirely replaced the completely necrotic areas. The newly reconstructed lobules, surrounded by fibrous tissue and containing the disarranged acini, showed a marked change from the picture seen two weeks previously (fig. 3 *B*). The misshapen acini were perhaps less deformed but were still made up of cells which varied markedly in shape and size; they took a nuclear stain much more readily than did those in specimens removed with a shorter postinjection interval. The central acinar granules (zymogen) were still diminished but took the oxyphil stain. The acinar cells appeared to be vitally efficient. No signs of regeneration of the acinar cells themselves were noted. Recovery of the acinar cells that still retained their nuclear membrane was the essential observation, with the formation of a bizarre type of lobule containing disarranged acini. What appeared to be proliferation of the duct epithelium was also noted. This conforms to Bensley's <sup>6</sup> conclusion. Microscopically, little change was seen after six and eight weeks that is different from the appearance in figure 3 *B*, except for greater solidity of the fibrosis and slightly more infiltration of lymphocytes and round cells. Sections of the omentum showed microscopically diffuse fat necrosis with hemorrhage, infiltration of polymorphonuclear cells and lymphocytes. Scattered areas of small focal abscesses were also noted in the omentum.

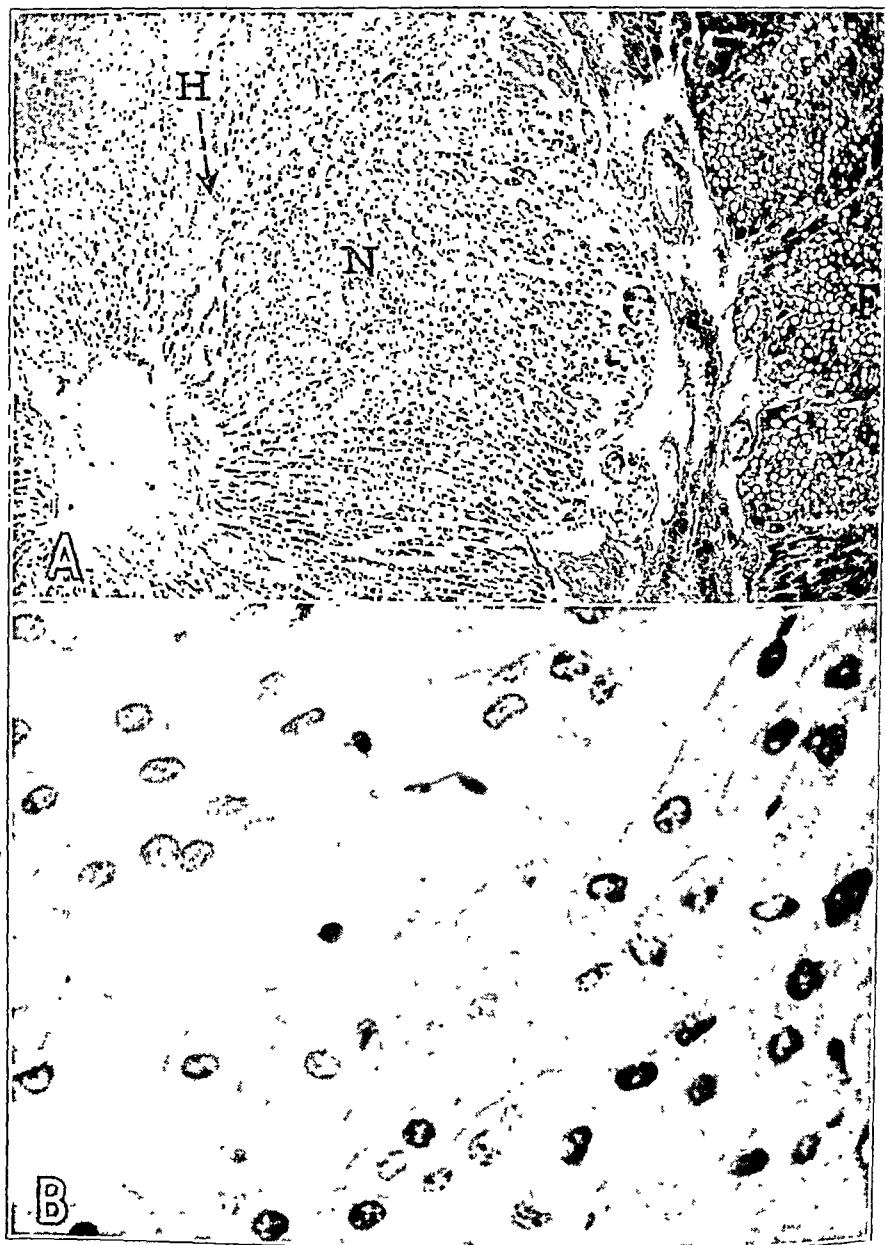


Fig. 4.—*A*, photomicrograph of the liver, showing necrosis and hemorrhage nine days after the production of the acute pancreatitis. The changes are diffuse and not localized to the central vein and periportal areas. *H* represents hemorrhage; *N*, cellular necrosis, and *F*, fatty infiltration. (Section taken one hour after death.) *B*, photomicrograph (high power) of the liver shown in *A*. Note the varying degrees of cellular necrosis. Edema, atrophy and vacuolation or fatty infiltration are present to a moderate degree.

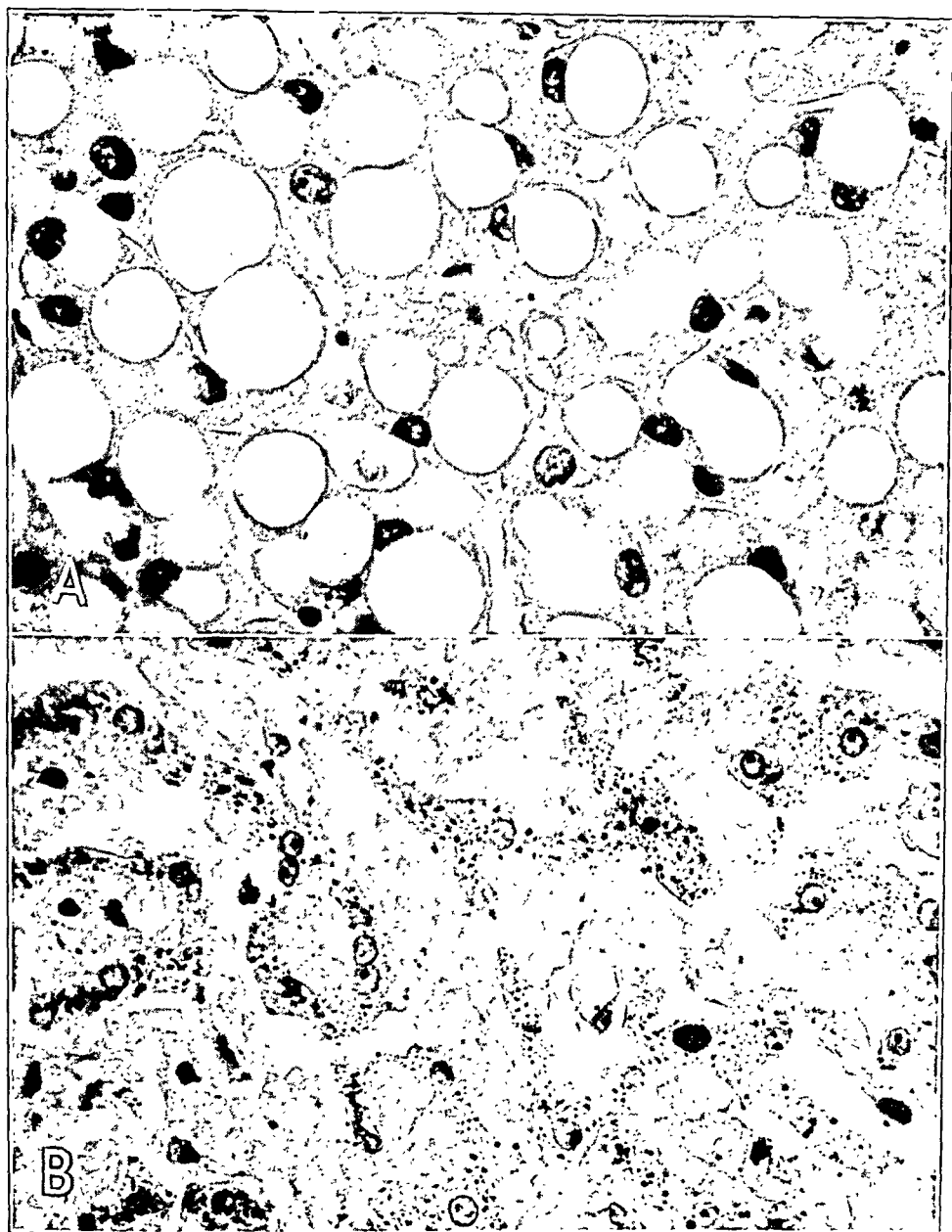


Fig. 5.—*A*, photomicrograph (high power) of figure 4 *A*, taken from the area of fatty infiltration. *B*, photomicrograph (high power) of the liver, representing a biopsy specimen taken forty-eight hours after the production of the acute pancreatic necrosis. Massive cellular necrosis with hemorrhage has taken place. Cords of injured cells remain. The animal died a few hours after the specimen was taken. (The pancreas showed microscopic changes of a much more severe grade than those depicted in figure 1.)



Although Whipple and Goodpasture<sup>18</sup> have reported that the fluid found in the peritoneal cavity of animals with acute pancreatitis is nontoxic, other observers speak of it as toxic. Many surgeons go so far as to justify a laparotomy on the basis of drainage of this material to the exterior before there has been opportunity for much absorption. It was because of this discrepancy in opinion as to the toxicity of the

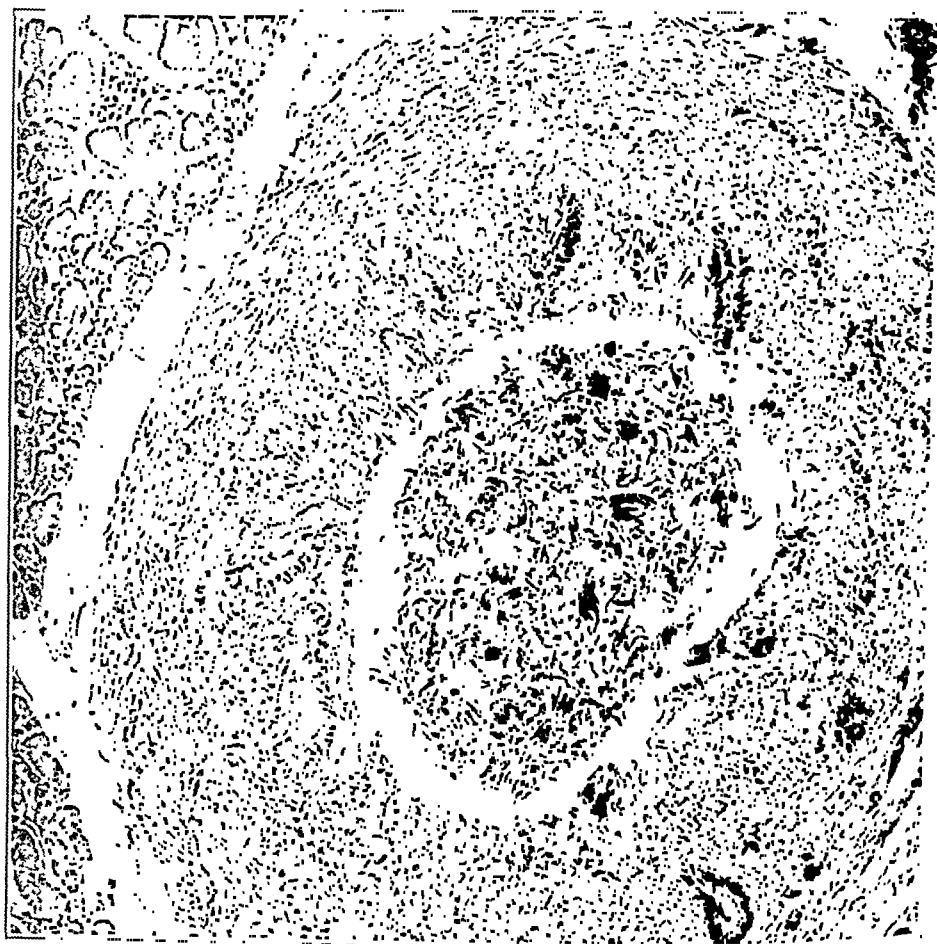


Fig. 6.—Photomicrograph of the pancreas taken fifteen days after injection, showing the wall of a large duct with complete loss of its lining epithelium and its lumen filled with cellular debris. In the wall of the duct are seen nests of epithelial cells of various sizes, with no definite pattern or shape. These were regarded as proliferating; the question arises whether these glands, which were presumably mucous in origin, are regenerating and will be the source of a newly formed epithelial lining for the duct. Since the duct was obviously patent at the time of removal of the biopsy specimen (fifteen days after injection), it would appear that, although the original lining epithelium was destroyed, the walls were viable, and a few of the cells on the surface were newly formed, arising from the mucous glands of the wall of the duct.

18. Whipple, G. H., and Goodpasture, E. W.: *Acute Hemorrhagic Pancreatitis*, Surg., Gynec. & Obst. **17**:541, 1913.

hemorrhagic fluid and its marked importance regarding indications for laparotomy that I made studies on the toxicity of the fluid. The toxicity was determined by injecting 2 to 3 cc. intraperitoneally into 10 white female mice weighing approximately 6 to 8 Gm. All of the mice lived and apparently suffered no ill effects, with the exception of 1. The mouse that succumbed, three days after the injection, was thought to have died from secondary infection, since peritonitis was observed at autopsy. Two dogs were given intravenous injections of the hemorrhagic exudate, 1 of 5 cc. and the other of 30 cc. Both were alive and well the next day and appeared to have suffered no ill effects. It would appear, then, that there may not be much justification for laparotomy for patients with acute pancreatitis if the primary object is to drain the hemorrhagic fluid to the exterior.

There is little information in the literature concerning the pathologic changes in the liver associated with acute pancreatitis. Focal necrosis of the liver occurring with pancreatitis of all types was noted by Archibald<sup>17</sup> in cats. The inability to determine cellular changes from the gross appearance of the liver conforms to clinical experience. About the only changes ever noted, grossly, consist of fatty infiltrations and an edematous edge, perhaps with a mottled appearance of the surface. Severe cellular changes may be found in a liver which appears relatively normal grossly.

The liver in all instances appeared little changed macroscopically, except for slight swelling, congestion and a dull red-gray color. Microscopically the liver in these experiments presented varying degrees of atrophy and edema around the central vein and the periportal areas, especially the former (fig. 4 *B*). The intensity of the pathologic changes in the liver was usually proportionate to the severity of the pancreatitis. The liver cords in the proximity of the central vein were narrowed, with widening of the adjacent hepatic sinuses, which contained erythrocytes and leukocytes together with cellular debris. The cytoplasm of the parenchymal cells was indistinct and contained vacuoles, the sharpness of the cell outline and the staining of the nuclei being much less than normal. In some of the more severe types of pancreatitis there was complete disruption of the liver cords, with cellular necrosis and massive hemorrhage; the nuclei showed pyknosis, karyorrhexis and karyolysis (fig. 5 *B*). In 2 or 3 cases, marked changes representative of fatty degeneration were noted (fig. 5 *A*). It is questionable whether the infiltration of fat in these livers was associated with pancreatic deficiency. I did not give lipocaic to any of the animals; this would no doubt have led at least to a tentative answer to the question.

From the animal that had 10 cc. of sterile bile injected into its pancreatic duct, sections of the liver were taken for microscopic study

six hours after injection. This animal, as has been mentioned, had a pancreas that was almost completely black and died a few hours after removal of the six hour biopsy specimen. Grossly, the liver appeared swollen and congested. Microscopically, one was impressed by the cellular changes produced in the liver six hours after the injection of 10 cc. of sterile bile into the pancreatic duct. The most striking change noted was the generalized edema, characterized by widening of the lymph spaces, as if the liver cords had been spread apart. The cytoplasm of the parenchymal cells showed evidence of cloudy swelling and was granular and pale staining. The nuclei also took the stain poorly but otherwise were essentially normal. Vacuoles in the cytoplasm were noted only occasionally.

The liver of 1 of the other animals microscopically had the appearance of central red atrophy, characterized by a partial disappearance of the liver cords and replacement with dilated blood-filled capillaries. The liver cells showed various stages of pyknosis of the nuclei, some karyorrhexis and breaking up of the cytoplasm. In some instances it appeared as if the capillaries had compressed the liver cords into narrow bands. There were massive edema and hyperemia throughout. It seemed that the severity of the pathologic changes produced was dependent on several factors, including the time element and the severity of the pancreatitis. The changes produced in the liver probably were characteristic of similar changes produced in other organs as part of the general reaction and toxemia. Although I believe that the hemorrhagic exudate was nontoxic, the aforementioned changes in the liver were probably the result of absorption by the blood stream of the toxic split protein products resulting from the necrosis of the pancreatic tissue.

#### COMMENT

In acute edematous pancreatitis the gland fully recovers in from ten days to two weeks, perhaps with slight residual edema, interlobular fibrosis and infiltration of a few lymphocytes. The gland can scarcely be differentiated from a normal gland. In the gland showing the next stage of parenchymal destruction, with patchy necrosis and hemorrhage, recovery occurs in a month, with the formation of a bizarre type of lobule containing disarranged acini, which, however, appear to function physiologically. Therefore, it should be emphasized that biopsy specimens taken more than ten days to two weeks after the onset of acute edema of the pancreas may show a practically normal gland and thus will not give an accurate indication as to the presence of pancreatitis a short time previously, as was suggested by Cole.<sup>19</sup> Furthermore, the patchy nature of the hemorrhage and necrosis may render

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19. Cole, W. H.: Acute Pancreatitis, New Orleans M. & S. J. 90:351, 1937.

diagnosis difficult, in that the biopsy specimen may be taken through the adjacent parenchyma, which is fairly normal (except for the edema), the essential pathologic process being missed (fig. 1).

#### SUMMARY

In this study on experimental animals, fat necrosis was observed in the 25 instances in which hemorrhagic or necrotic pancreatitis was present. Of the 15 animals with acute edematous pancreatitis, fat necrosis was observed in 8. This indicates that fat necrosis is most apt to be present with the more severe types of pancreatitis, a result conforming to clinical impressions.

The areas of complete necrosis obviously do not recover or regenerate; they are replaced by scar tissue, which may involve huge areas, as may be noted in the microscopic sections (fig. 2). In the edematous type of acute pancreatitis, slight residual edema and fibrosis with infiltration of lymphocytes were also seen. It is true, however, that a certain amount of induration (produced presumably by residual edema and slight fibrosis) may be encountered microscopically after the tissue has recovered.

Analyzing the microscopic data, I concluded that the acinar cells of the pancreas in acute pancreatitis tend to recover after damage (without complete destruction) and to become functionally efficient. This occurs with practically all types of pancreatitis, including those associated with patchy necrosis and hemorrhage. Cells which are damaged but retain their nuclear membrane intact will recover, usually with a disarranged lobular and acinar architecture.

The time required for recovery is about four weeks. The residual pathologic changes consist of interlobular and interacinar fibrosis with disarrangement of the acini, slight lymphocytic infiltration and perhaps slight edema. It is pointed out that erroneous impressions may be gained from biopsies because of the remarkable ability of the pancreas to recover (from the microscopic standpoint) within a short time, even though a moderate amount of induration may remain.

The hemorrhagic exudate in animals with acute edema hemorrhage or necrosis of the pancreas was shown to be nontoxic by the intraperitoneal injection of 2 to 3 cc. into white mice and by intravenous injection into dogs.

As far as I have been able to determine, the marked microscopic changes in the livers of animals with acute pancreatitis has not been emphasized previously, although Archibald<sup>17</sup> described it as having been observed in some of his experiments. This lesion is similar to that observed in other types of toxemia and consists primarily of generalized edema, cloudy swelling of the cells around the central vein and peri-

portal areas and necrosis. In some instances fatty degeneration, hemorrhage and extensive necrosis of the cells were noted. These conditions occurred in animals which were completely prostrated during the first twenty-four hours and presented a severe lesion of the pancreas with gross mass necrosis. This would suggest that hepatic insufficiency may be a significant contributory factor in the serious toxemia exhibited by many patients with acute pancreatitis. Whether or not the infiltration of fat in the liver (fig. 5A) is related to pancreatic deficiency (following pancreatectomy), as was shown experimentally by Fisher and Allan and their associates, cannot be determined. However, it would appear that there may be no particular relation, since such a short time (only two days) intervened between the pancreatic injury (produced by the injection) and the time of removal of the biopsy specimen from the liver. Since injection of bile into the pancreatic duct sometimes produced acute edematous pancreatitis and on other occasions caused acute hemorrhagic pancreatitis, it may be assumed that these two types of acute pancreatitis noted clinically are stages in the same process.

# CARCINOMA OF THE PANCREAS

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Over a hundred years has elapsed since carcinoma of the pancreas was first described as a clinical entity. In this period a considerable number of data have been accumulated relative to the course of the disease. However, as yet one is only rarely able to recognize it in its early phase. Furthermore, little progress has been made in the therapy of the condition; thus, carcinoma of the pancreas at present is one of the more discouraging medical problems. With the renewed interest in the cancer problem as a whole, the less common tumors become important problems for reconsideration. It is for this reason that we present this paper, in which we briefly review the development of the present knowledge of the disease; report on a series of patients, dealing in particular with the clinical course and the morbid anatomy as revealed at operation and autopsy, comparing our experiences with those of others, and, finally, discuss the treatment accorded carcinoma of the pancreas with specific reference to the possibilities of surgical therapy.

Mondière,<sup>1</sup> in 1836, described the cases of 2 patients in whom he recognized carcinoma of the pancreas. He referred to Morgagni as describing "scirrhus of the pancreas." Clute,<sup>2</sup> Leven<sup>3</sup> and Parmentier and Chabral<sup>4</sup> attributed the first clinical description to Mondière. Da Costa,<sup>5</sup> in 1858, collected 37 cases in which the patients died from carcinoma of the pancreas. He cited King, of Edinburgh, Scotland, as reporting in some detail on a patient with the same disease in 1827.

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From the Department of Surgery of the New York Hospital and Cornell University Medical College.

1. Mondière, J. T.: *Recherches pour servir à l'histoire pathologique du pancréas*, Arch. gén. de méd. **2**:36 and 265, 1836.

2. Clute, H. M.: The Problem of Cancer of the Pancreas, J. A. M. A. **107**: 91 (July 11) 1936.

3. Leven, N. L.: Primary Carcinoma of the Pancreas, Am. J. Cancer **18**:852, 1933.

4. Parmentier, E., and Chabral, E.: Les tumeurs solides du pancréas, in Roger, G. E. H.; Vidal, E., and Teissier, P. J.: *Nouveau traité de médecine, et de thérapeutique*, Paris, J. B. Baillière et Fils, 1923, pt. 15, p. 197.

5. Da Costa, J. M.: Cancer of the Pancreas, North. Am. Med.-Chir. Rev **2**:883, 1858.

Numerous contributions to the literature on this subject have followed, among the most important of which are those of Bard and Pic,<sup>6</sup> Mirallié<sup>7</sup> and Chauffard.<sup>8</sup> In 1888, Bard and Pic<sup>6</sup> described 7 cases of carcinoma primary in the pancreas, with verification by autopsy. They pointed out that the symptoms and signs which permitted ante-mortem diagnosis were progressive, persistent, painless jaundice, dilatation of the gallbladder, acholic stools and cachexia. Chauffard,<sup>8</sup> in 1908, discussed 2 cases of cancer of the body of the pancreas in which the chief symptom was pain. He described the characteristics of the pain and its shift from the left costal margin to the epigastric and periumbilical regions. This symptom was ascribed by the author to actual involvement of the solar plexus in the neoplastic process. The association of enlargement of the gallbladder and distention of the common duct in cases of noncalculous disease of the biliary tract was emphasized by Courvoisier<sup>9</sup> in 1890.

#### CLINICAL DATA

During the years 1932 to 1939 there were 38 patients among 28,600 admitted to the medical and surgical services of the New York Hospital who were considered to have carcinoma of the pancreas. Of these 38, the lesion was identified at operation or autopsy in 32, and their cases will constitute the basis for this clinical summary. In 17 instances the site of the neoplasm was identified at operation (in 3 it was confirmed by biopsy), while in 15 autopsy verified the diagnosis. The incidence of carcinoma of the pancreas in the New York Hospital was 1 in every 752 admissions, which agrees with other figures cited. Futcher<sup>10</sup> recorded a ratio of 1 pancreatic carcinoma in every 724 admissions to the Johns Hopkins Hospital; Kiefer,<sup>11</sup> 1 in every 864 admissions to the Peter Bent Brigham Hospital, and Leven,<sup>3</sup> 1 in every 1,780 admissions to the University of Minnesota Hospital. Ewing<sup>12</sup> stated that 1.76 to 2 per cent of autopsies on patients with cancer reveal a pancreatic neoplasm.

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6. Bard, L., and Pic, A.: Contribution à l'étude clinique et anatomopathologique du cancer primitif du pancréas, *Rev. de méd.* **8**:257, 1888.

7. Mirallié, C.: Cancer primitif du pancréas, *Gaz. d. hôp.* **66**:889, 1893.

8. Chauffard, M. A.: Le cancer du corps du pancréas, *Bull. Acad. de méd. Paris* **60**:242, 1908.

9. Courvoisier, L. G.: Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege, Leipzig, F. C. W. Vogel, 1890, p. 58.

10. Futcher, T. B.: Cancer of the Pancreas, *Tr. A. Am. Physicians* **34**:284, 1919.

11. Kiefer, E. D.: Carcinoma of the Pancreas, *Arch. Int. Med.* **40**:1 (July) 1927.

12. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1931, p. 745.

1. *Age and Sex.*—The age and sex incidences are remarkably constant in all published series. In our cases the ages of the patients ranged from 34 to 76 years. Twenty-five per cent were under 50 years of age, and 70 per cent fell in the age range of 50 to 69 years. The average age was 56 years, which corresponds to that noted by other investigators. Of our 32 patients, 23, or 72 per cent, were men, and 9, or 28 per cent, women. This agrees with the experience of others, for men are reported to be affected by the disease about twice as frequently as are women.

2. *Symptoms.*—The chief complaint as given by the patient was found most frequently to be pain. This is contrary to the usual textbook description of carcinoma of the pancreas but coincides with the findings of other investigators.<sup>13</sup> The chief complaints, in order of frequency, are given in table 1.

TABLE 1.—Symptoms in Cases of Carcinoma of the Pancreas.

Percentage			Percentage		
Pain.....	22	68	Anorexia.....	3	9.4
Jaundice.....	16	50	Loss of Weight.....	3	9.4
Vomiting.....	3	9.4	Weakness.....	2	6.3

TABLE 2.—Incidence of Symptoms

Percentage			Percentage		
Loss of weight*.....	31	97	Nausea.....	7	21.9
Pain.....	25	78	Constipation.....	7	21.9
Jaundice.....	18	56.2	Weakness.....	6	18.7
Anorexia.....	10	31	Diarrhea.....	4	12.5
Vomiting.....	9	28	Intolerance of fatty		
Itching.....	8	25	food.....	2	6.3
			Insomnia.....	1	3.1

\* Not mentioned in 1.

The distribution of symptoms irrespective of their order of appearance prior to admission, however, was somewhat different. In our series loss of weight was found to be almost constant. No mention of it was made in the case of 1 patient, but all the others reported a loss

13. (a) Duff, G. L.: *The Clinical and Pathological Features of Carcinoma of the Body and Tail of the Pancreas*, Bull. Johns Hopkins Hosp. 65:69, 1939. (b) Eusterman, C. B., and Wilbur, D. L.: *Primary Malignant Neoplasm of the Pancreas: A Clinical Study of Eighty-Eight Verified Cases Without Jaundice*, South. M. J. 26:875, 1933. (c) Grauer, F. W.: *Pancreatic Carcinoma*, Arch. Int. Med. 63:884 (May) 1939. (d) Hick, F. K., and Mortimer, H. M.: *Carcinoma of the Pancreas*, J. Lab. & Clin. Med. 19:1058, 1934. (e) Herringham, W. P.: *Primary Cancer of the Pancreas*, St. Barth. Hosp. Rep. 30:5, 1894. (f) Mussey, R. D.: *Pancreatic Carcinoma*, M. Clin. North America 3:681, 1919. (g) Rives, J. D.; Romano, S. A., and Sandifer, F. R., Jr.: *Carcinoma of the Pancreas*, Surg., Gynec. & Obst. 65:164, 1937.



of weight varying from 8 to 65 pounds (3.6 to 29.5 Kg.). The average loss prior to admission was 27.7 pounds (12.5 Kg.). Next in order of frequency was pain, with jaundice third. The incidence of the various symptoms is listed in table 2.

3. *Duration of Symptoms.*—The duration of symptoms prior to admission averaged four months and varied from one week to two years. One patient complained of pain on the left side on one occasion two years and on another occasion one year prior to admission. All the other patients had symptoms of less than one year's duration.

4. *Physical Examination.*—The pertinent physical abnormalities on admission are given in table 3. The most prevalent sign was jaundice, with enlargement of the liver second.

5. *Laboratory Data.*—Blood: The red cell count ranged from 2,500,000 to 5,200,000 per cubic millimeter, with an average of 4,200,000.

TABLE 3.—Physical Abnormalities

	Percentage			Percentage	
Jaundice.....	22	63	Abdominal tumor.....	6	19
Enlargement of liver..	17	53	Distended abdomen....	5	15.6
Abdominal tenderness..	12	37.5	Edema of extremities..	2	6.2
Palpable gallbladder..	11	34	Enlarged lymph nodes	2	6.2

The white cell count ranged from 5,500 to 16,400 per cubic millimeter, averaging 9,200, and the value for hemoglobin averaged 84.4 per cent, varying between 55 per cent and 110 per cent.

Stools: Eighteen, or 56.3 per cent, of the patients had clay-colored stools at some time during their course in the hospital. Seventeen, or 53.2 per cent, had stools which gave a positive benzidine reaction at some time during their stay in the hospital. This includes 2 patients who had occult blood only for three days postoperatively and 3 whose stool showed occult blood only once. In the majority of case records no statement was made as to the fat content of the stool or the bulk. When these were specifically mentioned it was only to record the absence of fatty or bulky stools.

Gastric analysis was performed in 11 cases. In 6 there was anacidity, in 4 hypoacidity and in 1 normal acidity. The patients with anacidity were aged 50, 56, 58, 60, 62 and 66 years, respectively. Those with hypoacidity were respectively 43, 56, 61 and 64 years old, and the patient with a normal concentration of acid was 68.

6. *Roentgen Reports.*—Gallbladder series were done in 6 cases. In 5 the organ was not visualized, and in the other a normal gallbladder was seen. Of the 5 organs not visualized, 4 were found to be markedly

distended at operation, and 1 was found at autopsy to be the seat of cholecystitis. The gallbladder that was visualized was found normal at operation.

Gastrointestinal series were done in 28 cases. In 14 a normal gastrointestinal tract was reported. Although defects were found in the other 14, a probable lesion of the pancreas could be identified by the roentgenologist in only 4 instances (14.3 per cent). The location of the defects is given in table 4.

A diagnosis of probable carcinoma of the stomach was rendered twice on the basis of the roentgenograms, as was a diagnosis of gastric ulcer. A report of a lesion extrinsic to the bowel, pressing on the duodenum, was made in 2 cases, but the radiologist did not consider that the changes warranted the diagnosis of carcinoma of the pancreas.

TABLE 4.—*Site of Lesion*

Pyloric end of stomach.....	.. . . .	4
First portion of duodenum....	.. . . .	1
Second portion of duodenum .	. . . . .	4
Third portion of duodenum ..	. . . . .	5
		—
		14

TABLE 5.—*Operations*

Cholecystogastrostomy .....	.. . . .	9
Posterior gastroenterostomy .....	.....	6
Exploratory laparotomy . . . . .	.....	3
Removal of biopsy specimen from pancreas.....	.....	3
Cholecystectomy and choledochotomy .. . . .	.. . . .	2
Cholecystoduodenostomy .....	.....	1
Gastroduodenostomy .....	.. . . .	1

7. *Operative Treatment.*—Of the 32 patients studied, 23 were subjected to operation, and on these patients twenty-five procedures were carried out. The types and number of operations are listed in table 5.

The 2 patients who were subjected to cholecystectomy and choledochotomy presented at the time of operation a lesion in the head of the pancreas which was firm but not stony hard. Calculi were found on exploration of the common duct, and it was felt that the pancreatic lesion was chronic pancreatitis. For this reason the gallbladder, which in each case was the site of inflammation, was removed.

In 1 of the patients the lesion was found so localized at operation that it was felt that resection in two stages would be feasible. Consequently, a cholecystogastrostomy and a posterior gastroenterostomy were performed, and postoperatively the patient was given pancreatin and lipocaic. Although the wound healed well, the patient lost ground

postoperatively, and it was felt that his condition was too hazardous to attempt the second stage. He died four months after operation.

8 *Location of the Lesion.*—Table 6 shows the location, according to the operative notes and autopsy records, of the neoplasm in the substance of the pancreas.

9. *Duration of the Disease.*—The duration was calculated from the time of appearance of the first symptom considered referable to the disease. The actual month of death was known for all but 2 patients, and in their cases it was reported to have been within a six month period. The average duration of symptoms was nine months, with extremes of

TABLE 6.—*Sites of Pancreatic Neoplasms*

Head	23	Head and body..	4
Body	1	Body and tail..	2
Tail	1	Entire gland...	2

TABLE 7.—*Invasion of Adjacent Structures (Autopsy)*

Duodenum . .	7	Splenic vein .....	1
Common duct. .	7	Capsule of spleen.....	1
Regional lymph nodes	5	Gallbladder.....	1
Stomach	2	Liver.....	1
The metastases were as follows:			
Liver . . . . .	8	Lungs .....	2
Retroperitoneal lymph nodes .	6	Diaphragm .....	2
Peritoneum.....	4	Pleura.....	2
Small intestine ..	4	Skull.....	1
Gallbladder...	3	Ribs.....	1
Adrenals...	3	Myocardium.....	1
Pylorus....	2	Axillary lymph nodes .....	1
Kidneys....	2	Tracheal bronchial lymph nodes	1
Omentum.	2	Large intestine.....	1

five weeks and forty months. Thirteen, or 39 per cent, of the patients had a total course of the disease, as indicated by symptoms, of three months or less.

10. *Extent of the Lesion.*—Of the 15 patients on whom autopsy was done, only 1 presented a lesion without local or distant extension of the growth. This was a man of 68 years, who had had intermittent jaundice for one year, with occasional cramps in the upper part of the abdomen. He lost 50 pounds (22.7 Kg.) in the year before admission. When first seen he was semicomatose, and he lived only nine days after admission. The growth involved the entire pancreas but had not extended beyond its capsule. There were numerous abscesses of the liver, as well as chronic cholecystitis, cholelithiasis and dilatation of the common bile duct. He had terminal bronchopneumonia.

The other 14 all showed local invasion of adjacent structures, and in 11 there were metastases. The sites and frequency of invasion are presented in table 7.

11. *Associated Abnormalities of the Biliary Tract.*—Abnormalities of the biliary tract seen at postmortem examination are presented in table 8.

## COMMENT

A point which deserves emphasis is that pain is the most frequent initial symptom of the disease and that jaundice runs a very poor second. Pain was the symptom first complained of by the majority of patients studied by Duff,<sup>13a</sup> Eusterman and Wilbur,<sup>13b</sup> Grauer,<sup>13c</sup> Hick and Mortimer,<sup>13d</sup> Herringham,<sup>13e</sup> Mussey<sup>13f</sup> and Rives, Romano and Sandifer.<sup>13g</sup> This is in agreement with our own data; pain was the chief complaint in 68 per cent of our cases and jaundice in 50 per cent. Only in the series of Ransom,<sup>14</sup> Rives, Romano and Sandifer<sup>13g</sup> and our own was jaundice the second most common initial symptom. Anorexia, nausea and vomiting were second in the lists of Eusterman and Wilbur,<sup>13b</sup> Grauer,<sup>13c</sup> Herringham,<sup>13e</sup> Hick and Mortimer<sup>13d</sup> and Mussey,<sup>13f</sup> whereas Duff<sup>13a</sup> found constipation to be next in frequency.

TABLE 8.—*Abnormalities of the Biliary Tract (Autopsy)*

Dilated common duct.....	11	Cholelithiasis.....	4
Cholecystitis.....	9	Choledocholithiasis.....	1

The importance of pain as the initial complaint in cases of carcinoma of the pancreas is contrary to most textbook descriptions of the clinical course of the disease. The phrase "painless jaundice" is often used in describing the typical clinical picture of carcinoma of the pancreas. Observers agree that pain is not only important and predominant but is often the first symptom of which the patient complains. In compiling the statistics from our own cases, the term pain was used only when specifically mentioned by the patient or by the person who took the history, who may be considered an unbiased observer. The terms "discomfort" and "distress" were not interpreted to mean pain and so were not included under that heading. The pain as described by the patient was usually dull and boring, often going through to the back. Ten patients located the pain in the epigastrium, and 10 stated only that it was abdominal. One patient complained of pain under the right costal margin and 1 of pain under the left costal margin.

It is of interest to note that the relative frequency of symptoms in the several clinical studies is practically the same in all. When loss of weight or emaciation is included as a symptom, it usually ranks as the most frequent (Duff; <sup>13a</sup> Futcher; <sup>10</sup> Hick and Mortimer; <sup>13d</sup> Kiefer; <sup>11</sup>

14. Ransom, H. K.: Carcinoma of the Pancreas and Extrahepatic Bile Ducts. *Am. J. Surg.* 40:264, 1938.

Lahey and MacKinnon;<sup>15</sup> Leven;<sup>3</sup> Ransom;<sup>14</sup> Rienhoff and Lewis<sup>16</sup>). Next in order is pain (Da Costa;<sup>5</sup> Duff;<sup>13a</sup> Eusterman and Wilbur;<sup>13b</sup> Fitcher;<sup>10</sup> Friedenwald and Cullen;<sup>17</sup> Grauer;<sup>13c</sup> Mussey;<sup>13f</sup> Reinhoff and Lewis<sup>16</sup>) or jaundice (Kiefer;<sup>11</sup> Mirallié;<sup>7</sup> Ransom<sup>14</sup>). Lahey and MacKinnon<sup>15</sup> listed anorexia as the most frequent symptom after loss of weight. In their series pain was third. In those series in which pain was second jaundice was third, and in those in which jaundice was second pain was third. Constipation was listed as an important symptom by Da Costa,<sup>5</sup> Duff,<sup>13a</sup> Kiefer,<sup>11</sup> Mirallié,<sup>7</sup> Leven<sup>3</sup> and Reinhoff and Lewis,<sup>16</sup> whereas Lahey and MacKinnon<sup>15</sup> stated that there was practically no disturbance in function of the bowel in their cases. Anorexia, weakness, nausea and vomiting are other prominent symptoms.

TABLE 9.—*Frequency of Distention of Gallbladder*

	Palpable, Percentage	Operation or Autopsy, Percentage	Operation, Percentage	Autopsy, Percentage
Mussey.....	..	..	83	..
Leven.....	70	..	86	..
Fitcher.....	67.7	..	..	..
Lahey and MacKinnon.....	..	..	64	..
Friedenwald and Cullen.....	62	..	..	..
Herringham.....	52.9	..	..	..
Kiefer.....	45.4	..	..	..
Hick and Mortimer.....	33	..	..	94
Rives, Romano and Sandifer.....	27	62	..	..
Grauer.....	20.6	..	..	..
.....	15	..	..	..
.....	34	..	60	..

The most common finding on physical examination was jaundice. This is confirmed in all series reviewed except that of Leven,<sup>3</sup> who listed emaciation first. Enlargement of the liver was mentioned by Duff,<sup>13a</sup> Grauer,<sup>13c</sup> Herringham,<sup>13e</sup> Kiefer<sup>11</sup> and Leven<sup>3</sup> as the next most frequent finding, and this was true in the series presented in this paper. Emaciation was listed as second by Ransom,<sup>14</sup> and a distended gallbladder was second in the series of Friedenwald and Cullen<sup>17</sup> and of Fitcher.<sup>10</sup> Because of Courvoisier's<sup>9</sup> emphasis on the association of the distended gallbladder and noncalculous biliary disease it is of interest to list the frequency of the distended gallbladder in the various clinical reports (table 9).

15. Lahey, F. H., and MacKinnon, D. C.: Carcinoma of the Pancreas, *S. Clin. North America* 18:695, 1938.

16. Rienhoff, W. F., and Lewis, D.: Surgical Affections of the Pancreas Met with in the Johns Hopkins Hospital from 1889 to 1932, *Bull. Johns Hopkins Hosp.* 54:386, 1934.

17. Friedenwald, J., and Cullen, T. S.: Carcinoma of the Pancreas: Clinical Observations, *Am. J. M. Sc.* 176:31, 1928.

This variation is marked, and no satisfactory explanation is evident. Enlargement of the liver may obscure distention of the gallbladder when it is present; or it may be that with many gallbladders found distended at postmortem examination the distention is developed during the later clinical course and therefore is not listed in the physical findings on first examination. Several of the series illustrate the fact that the gallbladder may be found distended at operation and yet not be detectable by palpation. This occurred in 5 of the 23 patients subjected to operation in our series. A further factor causing variation in statistics is the occurrence of cholecystitis in association with carcinoma of the pancreas. In 9 of our 15 autopsies (60 per cent) chronic cholecystitis was present, and

TABLE 10.—*Frequency of Palpable Tumor*

	Percentage
Hick and Mortimer.....	70*
Eusterman and Wilbur .....	60
Mussey .....	56
Rives, Romano and Sandifer.....	54†
Ransom <sup>18</sup> (lesions of body and tail).....	50
Friedenwald and Cullen .....	43
Futcher .....	39
Ransom <sup>14</sup> (head lesions) .....	38
Da Costa .....	35
Kiefer .....	27
Mirallié .....	20-25
This series .....	19
Duff .....	12.5
Herringham .....	12
Grauer .....	6
Leven .....	5.4

\* Including enlarged liver.

† Including enlarged liver and gallbladder.

according to the usual explanation of Courvoisier's law<sup>9</sup> this would tend to prevent this organ from responding by dilatation to the biliary obstruction.

The frequency of palpable tumor varied considerably (table 10).

These figures are not all strictly comparable, for, as has been indicated, in the series with the highest incidence, "tumor mass" has been employed in the broadest sense of the term. In the series with an incidence of 50 per cent and less, only the cases in which the primary neoplasm could be felt were included. In Eusterman and Wilbur's <sup>12b</sup> series a palpable tumor was eventually felt in 60 per cent of the cases.

Abdominal tenderness was mentioned as a sign in the series of Friedenwald and Cullen,<sup>17</sup> Leven,<sup>3</sup> Ransom <sup>18</sup> and Rives, Romano and Sandifer.<sup>13c</sup> Their figures agree with ours that this sign is frequent. Ransom observed it with the "majority" of lesions of the body and tail

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Lahey and MacKinnon;<sup>15</sup> Leven;<sup>3</sup> Ransom;<sup>14</sup> Rienhoff and Lewis<sup>16</sup>). Next in order is pain (Da Costa;<sup>5</sup> Duff;<sup>13a</sup> Eusterman and Wilbur;<sup>13b</sup> Futcher;<sup>10</sup> Friedenwald and Cullen;<sup>17</sup> Grauer;<sup>13c</sup> Mussey;<sup>13f</sup> Reinhoff and Lewis<sup>16</sup>) or jaundice (Kiefer;<sup>11</sup> Mirallié;<sup>7</sup> Ransom<sup>14</sup>). Lahey and MacKinnon<sup>15</sup> listed anorexia as the most frequent symptom after loss of weight. In their series pain was third. In those series in which pain was second jaundice was third, and in those in which jaundice was second pain was third. Constipation was listed as an important symptom by Da Costa,<sup>5</sup> Duff,<sup>13a</sup> Kiefer,<sup>11</sup> Mirallié,<sup>7</sup> Leven<sup>3</sup> and Reinhoff and Lewis,<sup>16</sup> whereas Lahey and MacKinnon<sup>15</sup> stated that there was practically no disturbance in function of the bowel in their cases. Anorexia, weakness, nausea and vomiting are other prominent symptoms.

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18. Ransom, H. K.: Carcinoma of the Body and Tail of the Pancreas. Arch. Surg. 30:584 (April) 1935.



of the pancreas<sup>16</sup> and in 59 per cent of cases of lesions of the pancreatic head and bile duct.<sup>11</sup> The other figures are those of Friedenwald and Cullen,<sup>17</sup> 70 per cent; Leven,<sup>3</sup> 66 per cent, and Rives, Romano and Sandifer,<sup>12a</sup> 55 per cent.

The occurrence of ascites varies widely; this condition was present in 62 per cent of Duff's<sup>13a</sup> series (lesions of the body and tail), in 11 per cent of Ransom's<sup>11</sup> and of Mirallic's<sup>7</sup> series and in 5 per cent of Leven's<sup>3</sup> cases. Edema was present in 15 per cent of cases by Fitcher<sup>10</sup> and by Ransom.<sup>14</sup> Ascites and edema were present terminally in 33 per cent of Friedenwald and Cullen's<sup>17</sup> patients. There were 15 per cent of patients with ascites and 6 per cent with peripheral edema in our series.

The blood picture is of no aid in diagnosis of carcinoma of the pancreas. When first seen, the majority of the patients present a normal blood picture, but as the disease progresses anemia usually develops.

Of our patients, 56 per cent had clay-colored stools and 53 per cent had stools which gave a positive benzidine reaction at some time during their stay in the hospital. This is in general agreement with the observations of Duff,<sup>13a</sup> Leven<sup>3</sup> and Ransom.<sup>14</sup> It should be emphasized here that examination of the stool for fat offers one of the most useful indexes for determining the absence of pancreatic juice in the intestinal canal; it should also be noted that increase in bulk of the stool or of its fat content was infrequent in most of the reported series, even when the normal flow of pancreatic juice was known to be compromised.

The results of gastric analyses in these cases are of interest; 10 of 11 patients (91 per cent) examined in our series had hypoacidity or anacidity. Other reports confirm this. Friedenwald and Cullen<sup>17</sup> reported 77 per cent; Ransom,<sup>14</sup> 71 per cent, and Grauer,<sup>13c</sup> 58 per cent, with lowered or absent free hydrochloric acid in the gastric content. Leven<sup>3</sup> noted anacidity in 50 per cent of gastric analyses in his cases of carcinoma of the pancreas. Mussey<sup>18f</sup> found free hydrochloric acid in 65 per cent of his cases. It should be pointed out that the majority of the patients fall into an age group in which hypoacidity is not infrequently present. Keefer and Bloomfield<sup>19</sup> found that anacidity was present in over 20 per cent of persons in the 50 to 60 year age period and in over 35 per cent of those beyond 60 years. This group did not present evidence of any anatomic disease.

It is generally agreed that carcinoma of the pancreas cannot, in the majority of cases, be diagnosed by means of the roentgen ray. Lahey and MacKinnon<sup>15</sup> reported, however, that in their series of 21 cases positive roentgen evidence of the lesion was present in 71.4 per cent

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19. Keefer, C. S., and Bloomfield, A. L.: The Significance of Gastric Acidity, *Bull. Johns Hopkins Hosp.* 39:304, 1926.

of the gastrointestinal series. Rives, Romano and Sandifer<sup>13g</sup> stated that 6 of 10 of their patients whose films were read at one hospital showed evidence of organic disease in the region of the pancreas and that in 16 of 40 cases a correct diagnosis was made from roentgenograms by the staff of another institution. Duff<sup>13a</sup> reported 30 per cent of pancreatic tail lesions as showing extrinsic defects in the gastrointestinal series, while lesions of the head gave defects in 40 per cent of gastrointestinal series and pyloric obstruction in 20 per cent. Ransom<sup>18</sup> stated that the radiologist suspected a pancreatic lesion in 25 per cent of the gastrointestinal series in his cases of carcinoma of the body and tail of the gland. In cases of carcinoma of the head of the pancreas or of the bile ducts<sup>14</sup> he reported that a pancreatic tumor was suspected in 17 per cent and diagnosed positively by roentgen study in 8.6 per cent. Leven<sup>3</sup> listed 12 per cent positive diagnoses and 12 per cent suggestive diagnoses of tumor in the region of the pancreas obtained in a series of 24 gastrointestinal studies on his patients with carcinoma. Hick and Mortimer<sup>13d</sup> stated that roentgen examination was "found to be of little help." Kiefer<sup>11</sup> reported no positive roentgen diagnosis in 13 cases of carcinoma of the pancreas. In our own cases the roentgenologist reported a probable lesion of the pancreas in 14.3 per cent of the gastrointestinal series, although defects were present in 50 per cent of the films.

Engel and Lysholm,<sup>20</sup> in 1933, advanced a method for roentgen delimitation of the pancreas. They did not claim that the pancreas can be directly visualized but stated that by displacement of the gas-filled stomach enlargement of the head or of the tail of the gland can be made evident. There has been, to our knowledge, no extensive use of this technic, and so no fair evaluation of it can be made at this time.

The neoplastic process is usually in the head of the pancreas; observers reporting more than 50 per cent of lesions observed by them to be due to carcinoma at this site are Eusterman and Wilbur,<sup>13b</sup> Fletcher,<sup>10</sup> Grauer,<sup>13c</sup> Kiefer,<sup>11</sup> Lahey and MacKinnon,<sup>15</sup> Leven,<sup>3</sup> Parmentier and Chabral,<sup>4</sup> Ransom,<sup>14</sup> Rienhoff and Lewis<sup>16</sup> and Rives, Romano and Sandifer.<sup>13g</sup> The next most frequent position of the growth was the entire gland in Grauer's,<sup>13c</sup> Lahey and MacKinnon,<sup>15</sup> Leven's<sup>3</sup> and Rienhoff and Lewis'<sup>16</sup> series and the body of the gland in Ransom's<sup>14</sup> cases. The region of the head and body was second in our own cases. Duff<sup>13a</sup> observed, in 14,000 autopsies at the Johns Hopkins Hospital, 28 neoplastic lesions in the head of the gland and 19 in the body and tail. He remarked that lesions of the head predominate in clinical reports and lesions of the tail in autopsy reports.

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20. Engel, A., and Lysholm, E.: Contribution à l'étude de la symptomatologie du cancer pancréatique, *Acta med. Scandinav.* 80:34, 1933.

The duration of life from the time of appearance of the first symptom to death averaged less than a year in all reports. This is unusual for a neoplastic process. Grauer<sup>13c</sup> reported 1 case of carcinoma of seven and 1 of five years' duration, but 28 of his 34 patients died within one year. By Duff<sup>13a</sup> the average was given as four and six tenths months for lesions of the head and five months for lesions of the body and tail. Ransom's<sup>18</sup> figure was ten and two tenths months for lesions of the body and tail. Kiefer<sup>11</sup> noted an average duration of life of seven and three tenths months after the first symptom. Leven<sup>2</sup> found little difference between the duration of life for the patients operated on and those not so treated, six and seven tenths months for the former group and six and one tenth months for the latter. Lahey and MacKinnon<sup>15</sup> stated that the average postoperative duration of life for 38 of their patients was eight and six tenths months, whereas for 8 patients who were given radiation therapy postoperatively the average was sixteen and eight tenths months. In the cases reported in this communication the average duration of life

TABLE 11.—*Operations for Relief of Biliary Obstruction*

Cholecystogastrostomy .....	9
Cholecystoduodenostomy .....	1
Cholecystectomy and choledochotomy .....	2

was nine months. The entire clinical course may be as short as five weeks, and it is exceptional for a patient to live more than a year after initiation of symptoms.

In our series of 32 patients, 23 were subjected to operation. Twelve of these had a procedure done to relieve the biliary obstruction (table 11).

Exploration to confirm the diagnosis and to determine inoperability was done in 3 instances. In 7 a shortcircuiting operation between the stomach and the duodenum or jejunum was done either for actual or for impending duodenal obstruction or as a preliminary step in anticipation of resection of the head of the pancreas. In 2 cases only was the complete preliminary operation done, and in none was the tumor resected.

Surgical therapy directed at carcinoma of the pancreas consists of two types of procedure, the first palliative and the second curative. The palliative operations have as their purpose the establishment of a communication between the gallbladder and the intestinal tract for relief of biliary obstruction. The first one stage cholecystogastrostomy was performed by Monastyrski<sup>21</sup> in 1887. This has been the operation of choice but unfortunately is frequently followed by cholangitis. In

21. Monastyrski, cited by Murphy, J. B.: Cholecysto-Intestinal, Gastro-Intestinal, and Entero-Intestinal Anastomosis, and Approximation Without Sutures (Original Research), M. Rec. 42:665, 1892.

a liver already damaged by lipid infiltration and hyaline degeneration, the addition of an infection may result in hepatic failure. However, there can be little doubt that certain patients owe a prolonged survival to cholecystogastrostomy which was not followed by cholangitis. Whipple<sup>22</sup> stated definitely that the incidence of ascending infection is diminished by employing a cholecystojejunostomy on the Roux principle, in which the fundus of the gallbladder is anastomosed to the cut end of the jejunum. Our study of several series leads us to the conclusion that palliative operations as a whole do not extend the life expectancy, although in the individual case they may appear to do so.

The curative type of operation provides for direct extirpation of the tumor. The most successful of these to date is that evolved by Whipple, Parsons and Mullins.<sup>23</sup> This procedure is carried out in two stages. The first consists of the establishment of a cholecystojejunostomy and a posterior gastroenterostomy. At the second stage of the operation the duodenum and the head of the pancreas are resected, and the divided end of the remaining pancreas is closed over after ligation of the duct. The external secretion of the pancreas is lost to the gastrointestinal tract, and the remaining pancreas tends to undergo fibrosis and atrophy. There has been increasing evidence in favor of conserving the external secretion of the pancreas, although this has been controversial for a long time. It would appear desirable, therefore, in a direct attack on this disease, to remove the tumor completely and to preserve the function of the remaining pancreas both for its internal and for its external secretions. This plan is by no means new, for it was stated by Desjardins<sup>24</sup> in 1907 that radical surgical treatment directed at the pancreas is dependent on restoration of a communication between the remaining pancreas and the intestine. This was the basis for a two stage procedure suggested by him for radical removal of a malignant lesion in the region of the head of the pancreas. These two stages consisted of (*a*) reestablishment of the continuity of the intestinal and biliary tracts and (*b*) resection of the duodenum and the head of the pancreas and restoration of the flow of pancreatic secretions by pancreaticojejunostomy.

The accomplishment of such a procedure has not, so far as we know, been described. Because of the success of transplantation of the end of the transected pancreas into the posterior wall of the stomach in dogs

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22. Whipple, A. O.: Surgical Treatment of Carcinoma of the Ampullary Region and Head of the Pancreas, *Am. J. Surg.* **40**:260, 1938.

23. Whipple, A. O.; Parsons, W. B., and Mullins, C. R.: Treatment of Carcinoma of the Ampulla of Vater, *Ann. Surg.* **102**:763, 1933.

24. Desjardins, A.: Technique de la pancréatectomie, *Rev. de chir.* **35**:945, 1907.

as done by Tripodi and Sherwin<sup>25</sup> and by Person and Glenn,<sup>26</sup> it is proposed that for tumors in the region of the head of the pancreas resection en bloc with the adjacent duodenum and regional lymph glands be performed. The transected end of the remaining portion of the gland may then be transplanted into the posterior wall of the stomach, thereby conserving the external secretion of the pancreas by directing it into the gastrointestinal tract. A new pathway for the bile may be established by a cholecystogastrostomy or a cholecystoenterostomy. A gastro-jejunosomy is then made to reestablish the continuity of the stomach and the intestine. The bleeding tendency associated with jaundice can be controlled, in the absence of extensive damage to the liver, by administration of dextrose, transfusions, bile salts and vitamin K. The liver may be additionally protected by the use of lipocaic or similar pancreatic preparations. With the patient thus adequately prepared and presumably protected from a bleeding tendency and impending failure of the liver, surgical removal of the tumor may be attempted, preferably in one stage. The postoperative course will undoubtedly be trying. However, utilizing the same armamentarium that has been employed to prepare the patient, namely, dextrose, transfusions and vitamin K, one may anticipate some measure of success.

#### SUMMARY

An analysis is presented of the clinical and laboratory data in 32 cases of carcinoma of the pancreas proved by operation, autopsy or both.

The incidence was 1 in every 752 medical and surgical admissions to the hospital.

The age of the patients ranged from 34 to 76 years, with an average of 56. Seventy-two per cent of the patients were men; 28 per cent, women.

The most common chief complaint, as stated by the patient, was pain, which was present in 68 per cent of the patients. The second chief complaint, jaundice, was reported by 50 per cent of the patients.

Loss of weight was mentioned by 97 per cent of the patients on admission; pain had been experienced by 78 per cent of them, and jaundice had been present in 56 per cent.

The average duration of symptoms prior to admission was four months.

On physical examination, the most frequent finding was jaundice, which was mentioned in 68 per cent of cases. The liver was enlarged in 53 per cent of the patients, and a distended gallbladder was palpable in 34 per cent.

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25. Tripodi, A. M., and Sherwin, C. F.: Experimental Transplantation of the Pancreas into the Stomach, *Arch. Surg.* **28**:345 (Feb.) 1934.

26. Person, E. C., Jr., and Glenn, F.: Pancreaticogastrostomy: Experimental Transplantation of the Pancreas into the Stomach, *Arch. Surg.* **30**:530 (Oct.) 1939.

Fifty-six per cent of the patients had clay-colored stools, and in 53 per cent the stools gave a positive benzidine reaction at some time during the course in the hospital.

Gastric hypoacidity or anacidity was present in 91 per cent of 11 patients examined.

Fifty per cent of the gastrointestinal series showed no defects. In 14 per cent of the remainder a lesion of the pancreas could be identified.

Of the 32 patients, 23 were operated on, and 17 had short-circuiting procedures done.

The lesion was found to be in the head of the gland in 27 instances, in the body in 7 and in the tail in 3.

The total duration of the disease, as indicated by symptoms, averaged nine months.

The sites of local invasion and metastases are listed.

A comparison of these data with those found in the literature is presented.

The present status of surgical therapy is discussed, with special reference to the curative type of operation.

It is suggested that in favorable cases a radical type of procedure might be performed in one stage, with conservation of the external secretion of the pancreas.

## PRIMARY APPENDICAL ABSCESES

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AND

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Acute appendicitis is a tantalizing disease, for it unremittingly exacts an exorbitant toll of human lives. The challenges presented by that unpredictable organ, the appendix, are legion; hence this discussion will be confined to acute appendicitis complicated by primary abscess formation. Bower,<sup>1</sup> in his commendable study, found that 15 per cent to 20 per cent of all patients admitted to the Philadelphia Hospitals for acute appendicitis had localized abscesses when first seen. Arnheim and Neuhof<sup>2</sup> reported an incidence of 18.8 per cent, and Guerry<sup>3</sup> encountered this complication in 18 per cent of his 3,339 cases of "acute suppurative appendicitis." If the appendicitis, however, occurred in patients beyond 59 years of age, Wood<sup>4</sup> found that 56 per cent of them had regional abscesses. In our series of 528 cases of acute suppurative appendicitis there were 53 primary abscesses, a ratio of 10 per cent. This low incidence is accounted for by the fact that these patients were recruited largely from private practice and not reported on from the records of charitable institutions. According to authentic reports, at least 20 per cent of patients suffering from acute appendicitis have regional abscesses prior to their admission to the hospital. If one were to include those cases of regional peritonitis in which the process of localization has not had time to become complete before the surgeon intervenes, the incidence would be much higher.

The position of the appendix and the point at which the pathogens penetrate its walls largely determine the location of the primary abscess. Appendical abscesses may be conveniently classified as pericecal, sub-

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1. Bower, J. O.; Burns, J. C., and Mengle, H. A.: Induced Spreading Peritonitis Complicating Perforating Appendicitis, *Surg., Gynec. & Obst.* **66**:947-961, 1938.

2. Arnheim, E. E., and Neuhof, H.: The Severer Forms of Acute Appendicitis with Special Reference to the Treatment of Appendiceal Abscess, *Surg., Gynec. & Obst.* **70**:42-47, 1940.

3. Guerry, L.: A Study in the Mortality of Appendicitis, *Ann. Surg.* **84**:283-387, 1926; in discussion on Shipley, A. M., and Bailey, H. A.: Treatment of Appendicitis Complicated by Peritonitis, *ibid.* **96**:537-550, 1932.

4. Wood, C. B.: Acute Appendicitis in the Aged, *Am. J. Surg.* **26**:321-325 1934.

hepatic, subphrenic, ileocolic and pelvic (fig. 1). Regional structures, such as the cecum, small intestines, colon, liver, omentum, mesentery, bladder, generative organs and abdominal wall, may assist in localizing the suppurative process.

#### PERICECAL ABSCESES

At least 75 per cent of all primary appendical abscesses are contiguous with the cecum, the pus being confined to the right flank, the

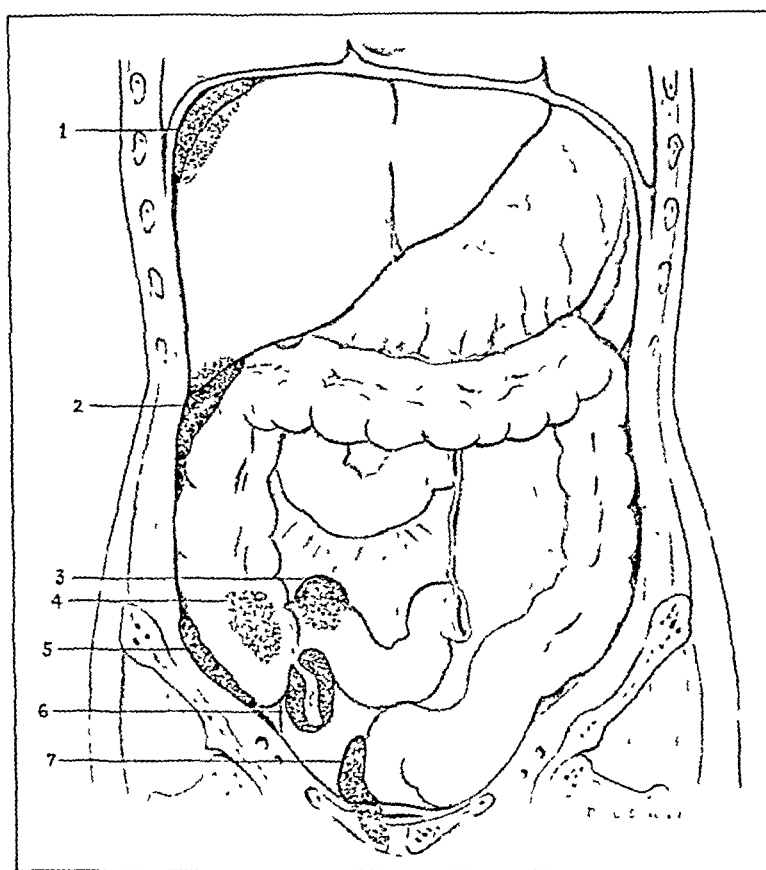


Fig. 1.—Location of primary appendical abscesses: 1, subphrenic; 2, subhepatic; 3, ileocolic; 4, retrocecal; 5 and 6, pericecal (right flank; right iliac fossa); 7, pelvic.

right groin or the retrocecal area. The appendix, being the provocative focus, is always connected with the pyogenic collection. It may be so completely embedded within the confining walls of the abscess that its position is difficult to determine, or the entire organ or any segment of it may project into the pyogenic cavity. Cases have been reported in which the "gangrenous appendix was completely detached from the cecum and was found floating in the pus," but in our experience the necrotic organ has always been anchored by the cecum or the meso-



appendix. Complete disintegration and autolysis of the appendix have been reported much more frequently than they really happen, for, like Arnheim and Neuhoﬀ,<sup>2</sup> we have operated on patients whose previous operative record stated that "the appendix had sloughed and could not be found," only to find the elusive organ firmly buried in a dense mass of adhesions but still attached to the cecum.

Operative and postmortem studies furnish ample evidence that these circumcecal abscesses tend to be multiple. They may form several isolated pockets or may fuse and produce a multilocular abscess. This was demonstrated in the case of a 76 year old woman who presented herself with a large tender mass in the right flank. A large pericecal abscess was encountered, and 100 cc. of foul-smelling pus was evacuated, but only one segment of the tumor collapsed. Exploration of the internal surface of the cavity with a sterile light disclosed a small stream of pus entering its lateral wall. The small orifice was gently dilated, and an additional 175 cc. of material was aspirated from a communicating pocket. Strangely enough, both loculi had patulous communications with a necrotic, fecolith-laden appendix. Retrocecal infections are prone to extend along the posterior surface of the ascending colon and invade the perinephric and subhepatic areas. Undoubtedly many of the so-called postoperative, or secondary, abscesses are nothing more than two or more isolated foci which were overlooked during the initial exploration. Failure of the patient to respond to evacuation of one purulent focus should strongly suggest the presence of a sequestered companion.

The clinical manifestations of pericecal abscesses are confusing, for they may develop during the first twelve hours of infection, particularly in children, or they may not become evident for several days. The only deviation from the initial symptoms of appendicitis are increasing hyperthermia, progressive toxicity and increased leukocytosis. In the cases of uncomplicated acute appendicitis, the average leukocyte count was 12,500 per cubic millimeter, as compared with 18,500 for those in which regional abscesses developed.

Retrocecal abscesses may produce intense ureteritis, pyuria and lumbar intumescence which strongly suggests a perinephric abscess of renal origin. In 1 instance 510 cc. of pus was drained from a large perirenal abscess, but the resulting lumbar fistula refused to heal, and it was not until a contrast roentgenogram demonstrated that the fistulous tract communicated with a patulous appendix that the true sequence was understood. Removal of the provocative appendix resulted in complete recovery. In another case the patient complained of troublesome pyuria for which he had undergone numerous dilations of the right ureter with lavages of the renal pelvis and a transurethral resec-

tion of the prostate gland, but to no effect. Intravenous pyelograms disclosed a ureteral fistula connecting a retrocecal abscess with the appendix. After removal of the perforated appendix and drainage of the retrocecal abscess, the ureteral fistula healed spontaneously, the functional integrity of the right kidney being thereby preserved.

Physical examination is very informative, as it usually discloses a tender, fixed mass in the right flank or groin. On several occasions abscesses were suspected, but exploration revealed a nonperforated appendix securely wrapped in the protective folds of the omentum. Fluctuation can rarely be demonstrated, as the spasticity of the overlying muscles and the induration of contiguous structures obscure the fluid wave. Peristalsis is usually diminished or absent over the affected area but is increased or normal throughout the other quadrants. Subsequent auscultations fail to show any extension of the "silent zone," a most valuable sign in differentiating spreading peritonitis from regional abscess.

Many pericecal abscesses lie contiguous to the anterior abdominal wall and can be safely explored by the extraperitoneal route. The incision should be placed directly over the intumescence, so that the pus can be aspirated and the offending appendix removed. It is well to remember, however, with the retrocecal variety and occasionally with the subcecal type, that the intestines form the anterior covering of these deep-seated abscesses, and any attempt to drain them through a stab puncture may injure the intestines and produce a fecal fistula. Whenever such a condition is encountered, the incisions should be large enough to afford ample exposure, so as to minimize accidental trauma.

If the appendix lies adjacent to the cecum the infectious process invades the cecal wall, rendering it rigid, friable and edematous. Not infrequently, necrotizing cecitis supervenes and greatly complicates the surgical problem. Attempts to close the defect made by removing the appendix constitute a challenge much akin to that encountered in closing a perforated gastric ulcer. The succulent cecal wall is too rigid to be plicated or inverted, and any attempt to ligate the stump of the appendix is futile, as the ligatures readily cut through the spongy tissues. In such cases we have merely sutured the omentum or the mesentery over the cecal defect (fig. 2), and in 3 instances we have encountered no residual infection. If there is a scarcity of omental or mesenteric tissues, a simple cecostomy tube is inserted through the stump of the severed appendage. As soon as the cecitis subsides, the tube is removed, which permits the fistula to close spontaneously.

In 39 of 40 cases of pericecal abscesses we have removed the appendix at the primary operation, and we feel that by so doing we have materially reduced the morbidity and mortality rates. If the patient is extremely

toxic, and particularly if there is a large retrocecal abscess, it seems much safer to drain the purulent collection through Petit's triangle and remove the appendix at a later date.

#### SUBPHRENIC AND SUBHEPATIC ABSCESSSES

Upward extension of the pericecal infection, either by contiguity or by means of the lymphatics, accounts for many subphrenic abscesses. The process of localization does not occur until eight or ten days after

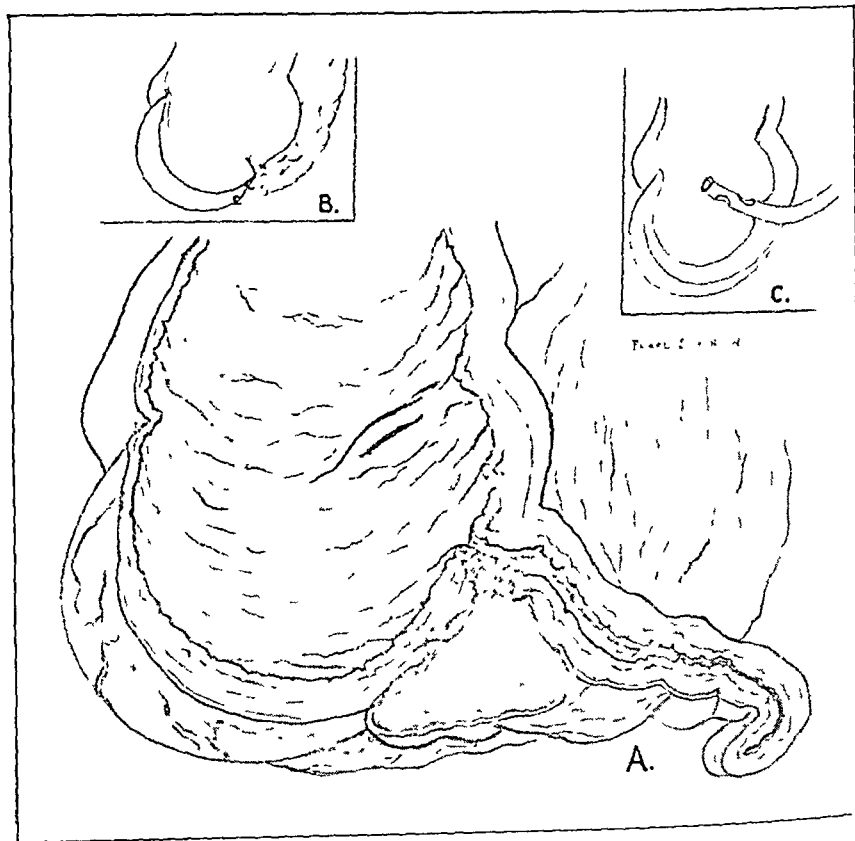


Fig. 2.—*A*, ruptured appendix forming a pericecal abscess associated with severe gangrenous cecitis. *B*, closing of a cecal defect with mesoappendix or omental tissue. The necrotizing cecum is so friable that the opening cannot be sutured. *C*, method of inserting a drainage tube through the appendical stump when the cecal defect cannot be closed.

onset of the primary infection or an equal period after the operation. The patients are very toxic and complain of pain over the lower part of the right side of the chest and in the right supraclavicular area. Examination demonstrates definite tenderness over the twelfth rib, accompanied with diminution of respiratory excursions. Fluoroscopic studies reveal a "high-fixed" diaphragm and occasionally a concomitant

pleural effusion. Diagnostic aspirations are mentioned only to condemn them as purveyors of infection. The pus is usually confined to the right posterosuperior space above, or the right inferior area below, the liver. Occasionally, however, multiple foci are encountered.

If one suspects a subphrenic abscess, it should be explored by the posterior extraserous route as advocated by Ochsner and DeBakey.<sup>5</sup> While this requires resection of the twelfth rib, it certainly prevents contamination of the pleural sac and provides dependent drainage. If one discovers an unsuspected subphrenic abscess during the primary operation, it should be drained through the posterior extraserous route, entirely independent of the appendical infection. Attempts to drain these abscesses through the appendical incision, against the force of gravity, has resulted in residual sequestrations which later develop into troublesome secondary abscesses. Deaver<sup>6</sup> strongly emphasized the wisdom of adequate drainage and insisted that many of these abscesses are overlooked during the initial operation.

#### ILEOCOLIC ABSCESES

The most treacherous variety of appendical abscesses are those which lie mesial to the cecum, being enmeshed in the coils of the ileum and its mesentery (fig. 3). The concomitant ileitis so alters the clinical picture that it may be mistaken for severe gastroenteritis, acute dysentery, intestinal obstruction or intussusception. The delay involved in making a correct diagnosis permits the abscesses to become rather large before they are recognized.

There are several reasons why these ileocolic abscesses are extremely dangerous. 1. Kinks, adhesions and inflammatory edema may precipitate an acute intestinal obstruction, thus complicating an already serious condition. 2. If the suppurative process lies adjacent to the mesenteric vessels, it may produce thrombophlebitis, with resulting segmental gangrene of the ileum, or ascending pylephlebitis. 3. These deep-seated abscesses may rupture spontaneously, thus evoking fulminating peritonitis. 4. Owing to the intra-abdominal position of the abscesses, one has to traverse a clean peritoneal space before the troublesome pus can be evacuated.

These dangers can be greatly minimized by active conservatism, for surgical intervention must be judiciously timed. If one interferes before nature has completed her program of isolation, the infection is disseminated and the "operatively induced peritonitis" carries a forbidding

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5. Ochsner, A., and DeBakey, M.: Subphrenic Abscess: A Collective Review and Analysis of 3,608 Collected and Personal Cases, *Internat. Abstr. Surg.* **66**:426, 1938; in *Surg., Gynec. & Obst.*, May 1938.

6. Deaver, J. B.: Appendiceal Peritonitis, *Surg., Gynec. & Obst.* **47**:401-405, 1928.

mortality. On the other hand, prolonged passivism is not without danger, for 2 of our patients were admitted to the hospital with fulminating peritonitis caused by spontaneous perforation of ruptured appendicoilomesenteric abscesses. Intervention had evidently been postponed too long.

Evacuation of these abscesses can be accomplished without contaminating the clean peritoneal spaces provided the purulent focus has been properly sequestered by protective moist packs before the pus is aspirated (fig. 4). This affords complete visualization of the operative field, permitting the aspirator to be inserted into the presenting part of the abscess without injury to the inflamed but succulent bowel. Bower<sup>1</sup>

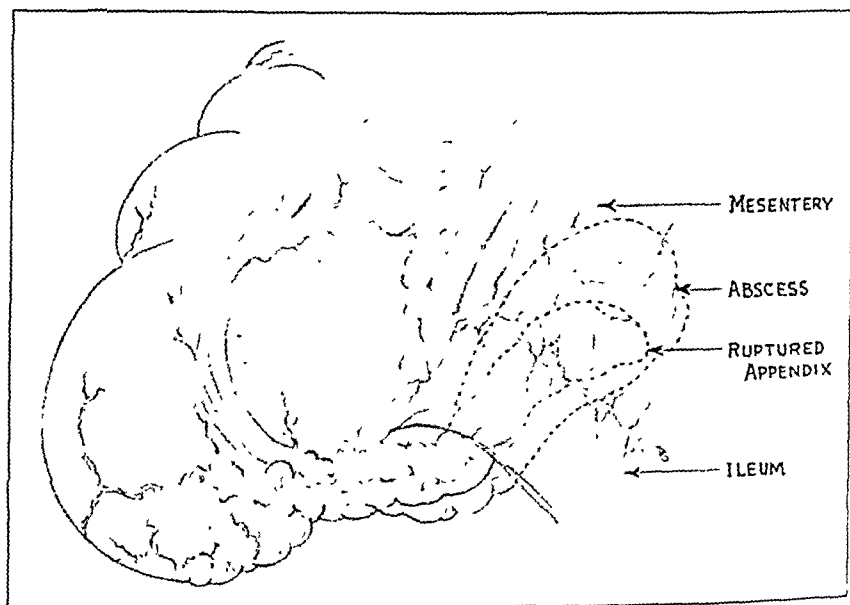


Fig. 3.—Ruptured appendix forming an ileomesenteric abscess, which frequently produces ileitis, intestinal obstruction or pylephlebitis.

has wisely emphasized the danger of inserting an inquisitive finger through a small abdominal incision in quest of these elusive abscesses. He correctly maintained that the "operatively induced peritonitis" is usually fatal.

Unless the appendix is readily mobilized, no attempt should be made to remove it. Dissection of the embedded appendix from adherent loops of inflamed intestine merely destroys nature's confining barriers and actually disseminates the invading pathogens. Decompression of the tense abscess usually restores the vascularity of the bowel to its normal level, thereby preventing gangrene, and alleviates the impending obstruction. If necessary, a decompressive ileostomy can be employed, but judicious use of the Wangenstein suction and the Abbott-Miller intestinal intubation has greatly reduced the necessity for this added

surgical insult. The appendix should be removed during a quiescent period, for the infective nidus may erupt and precipitate another abscess. This has happened in 2 of our cases.

#### PELVIC ABSCESES

Clinically, there are four different types of abscesses of the cul-de-sac. With one variety, the diseased appendix hangs over the brim of the

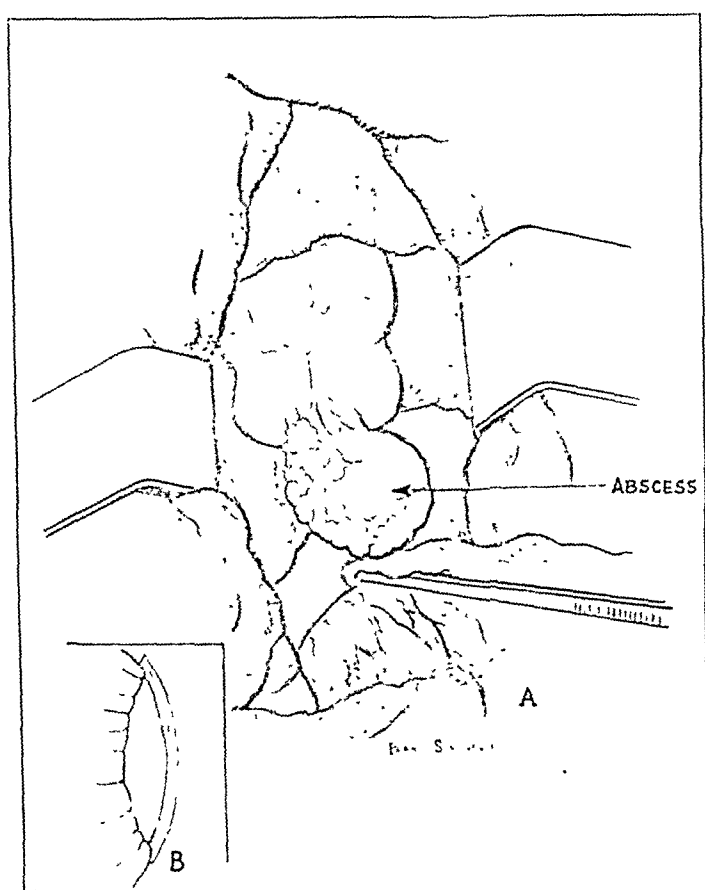


Fig. 4.—*A*, method of sequestering the abscess with protective packs before evacuating the pus. *B*, rubber dam anchored to the peritoneum so as to protect the margins of the wound from contamination during the evacuation. This is overlaid with gauze.

pelvis and empties the cecal contents directly into the pouch of Douglas. With the second form, the pericecal infection succeeds in soiling the cul-de-sac before localization has taken place, and when nature's defensive forces have been completely mobilized two distinct abscesses form, one around the cecum and the other in the pelvic cavity. With the third type, there is a fistulous communication between the pericecal abscess and that in the cul-de-sac. In the last type, the collection of pus within

the pelvis occurs as part of the generalized peritonitis. Recognition of the various types is essential to correct therapy.

Pelvic abscesses produce an intense irritation of the anterior rectal wall, causing an annoying tenesmus, a persistent watery diarrhea and constant perineal distress (fig. 5). Haggard<sup>7</sup> maintained that the hydromucoid diarrhea should always suggest the possibility of a perisigmoidal abscess. Examination discloses a patulous anus, due to loss of sphincteric tone, and a tender but fluctuant mass impinging on

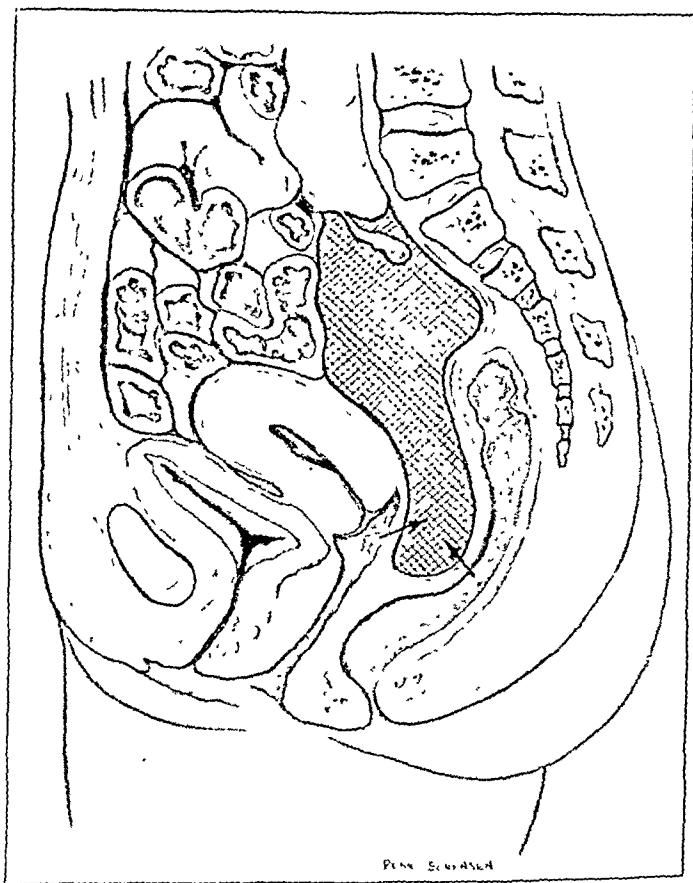


Fig. 5.—Pelvic abscess. The arrows indicate the points at which vaginal or rectal drainage can be instituted.

the anterior rectal wall. Proctoscopically the mucosa appears inflamed, edematous and succulent, and one has no difficulty in locating the "softening area" at which the abscess is pointing. In children, the cul-de-sac is so shallow that the inflammatory mass can usually be felt suprapubically. Rectal examinations are always informative and should be made before appendectomy is performed, as many unsuspected abscesses of the cul-de-sac will thus be discovered.

7. Haggard, W. D.: Appendicitis, *Am. J. Surg.* 28:71-77, 1935.

Ochsner and Murray<sup>8</sup> estimated that only 25 per cent of pelvic abscesses require surgical drainage, the majority being absorbed spontaneously. There is no doubt, however, that the morbidity could be greatly reduced were surgeons not so timid in draining these incarcerated collections of pus. The absorption of toxic substances involved, combined with the associated avitaminosis, hypoproteinemia and dehydration, effectively depletes the patient's physical reserves. Evacuation of these abscesses minimizes such complications. The use of retention enemas of warm oil and the application of diathermy promote spontaneous absorption of the smaller abscesses and facilitate localization of the larger pockets.

In women most abscesses of the cul-de-sac can be effectively and safely drained through the vagina (fig. 5). Such a procedure must be reserved, however, for those cases in which the pus lies contiguous to the posterior fornix, for if the intestines lie between the abscess and the vaginal septum they may be accidentally incised. Two patients with such a condition were admitted to the hospital, and correction of the resulting enterovaginal fistulas was most difficult. Localization and drainage of these abscesses should always be done under colposcopic vision. The drainage sinus must be of sufficient size to permit complete evacuation of the liquid pus and the fibropurulent debris. Much of this material can be removed by irrigating the pyogenic cavity at the time it is opened. This procedure is painless and can be carried out each day until the pyogenic pocket is completely obliterated.

It is well to remember that the small intestines are the natural inhabitants of the pelvic cavity and necessarily form some portion of the restricting abscess wall. The distended intestines usually float on top of the purulent collection, but they may dip down into or completely encircle the suppurative focus, thus making it inaccessible. Likewise, the female generative organs may become involved in the inflammatory process, and if the abscess is encased by the intestines or involves the ovaries it is advisable to explore the infected area from the abdominal route. This provides clear visualization of the involved structures and permits evacuation of the pus without injury to regional organs. In the vast majority of cases the appendix can be safely removed and the abscess drained through the posterior vaginal wall.

In young children and in males, pelvic abscesses can be most effectively drained through the rectum (fig. 5). The pus is first located by inserting an aspirating needle under proctoscopic vision into the presenting part of the abscess. With the needle as a guide, an incision is made into the anterior rectal wall in a longitudinal direction, so as to avoid the main hemorrhoidal vessels, which course along its lateral margins. The opening is then gently dilated by blunt forceps until it

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8. Ochsner, A., and Murray, S.: Appendicitis, *Am. J. Surg.* **46**:566-583, 1939



is large enough to afford adequate drainage. Some authors<sup>8</sup> affirm that effective drainage can be maintained only if the rubber drain is anchored to the abscess and brought out through the anus. This procedure seems unnecessary, because (1) the peristaltic action of the bowel effectively collapses and evacuates the abscess;<sup>9</sup> (2) the drains act as a foreign body, irritating the inflamed mucosa and enhancing the tenesmus, and (3) these drains must be sutured to the rectal wall if they are to be held in place, and this predisposes to fistula formation.

Many secondary abscesses of the cul-de-sac result from indiscriminate exploration of the pelvic cavity during removal of an acutely inflamed appendix. The virulent pathogens are carried to the unsoiled pelvic structures by the inquisitive fingers or by the exploring aspirator in the search for a suspected abscess. Such thoroughness is commendable, but the same information can be obtained from a preoperative rectal examination.

#### PLYLEPHLEBITIS

Extension of the inflammatory process to the portal vein ushers in the serious complications of pylephlebitis and portal thrombosis. They occur in 1 per cent to 3 per cent of all cases of acute appendicitis and in 5 per cent of patients subjected to appendectomy. Chills, fever, icterus and biliuria are the ominous warnings that the infection has spread to the portal system. On laparotomy the appendix is found to be swollen, turgid and acutely inflamed, while the ileocolic vessels exhibit evidence of thrombophlebitis. Stewart-Wallace<sup>10</sup> emphasized the value of performing primary ligation of the involved ileocolic vessels at the same time the appendix is removed. He reported recovery in 3 of his cases after adhering to this principle of active prophylactic intervention.

When the pylephlebitis occurs after the appendectomy, it may do so immediately or it may be delayed for five to six weeks. Usually the patient has been doing well until the catastrophe strikes, and then pains in the upper right abdominal quadrant, jaundice, septic reaction and chills suddenly announce the onset of this complication. The difficulty in establishing an early diagnosis and the hesitancy to reexplore the abdomen of these septic patients account for a death rate of approximately 85 per cent. Intervention can be postponed too long, as was demonstrated in 2 nonoperative cases in which the patients died immediately after admission to the hospital. At autopsy, multiple abscesses were observed along the course of the ileocolic vessels and in the subphrenic area. When the portal vein was opened, numerous

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9. Vale, C. F.: Postappendiceal Abscess in Rectovesical Pouch: Transrectal Drainage, *Ann. Surg.* **111**:396-402, 1940.

10. Stewart-Wallace, A. M.: Pylephlebitis Complicating Appendicitis and Its Treatment by Ligation of the Mesenteric Veins, *Brit. J. Surg.* **23**:362-376, 1935.

mycotic emboli were found attached to its walls, thus accounting for the origin of the septic thrombi which had produced the multiple abscesses of the liver (fig. 6). Early exploration, drainage of the regional abscesses and ligation of the involved venous radicles, combined with intensive chemotherapy, offer the only hope of succor.

#### PREOPERATIVE MANAGEMENT

Primary appendical abscesses never present such an emergency that time cannot be taken to prepare the patient for the surgical insult.

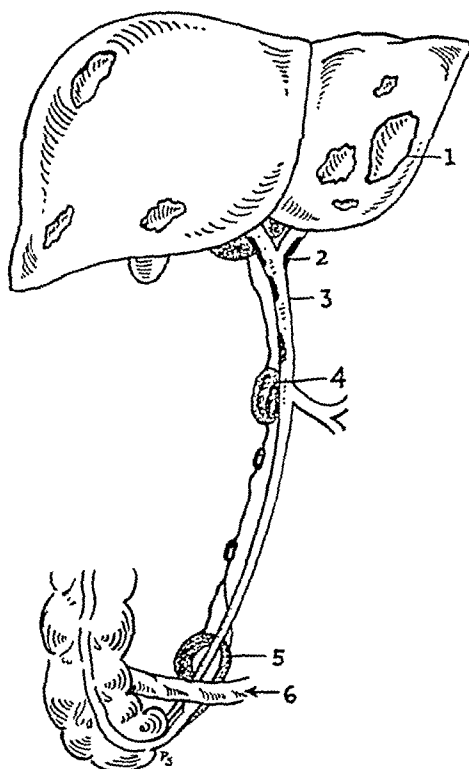


Fig. 6.—Ileomesenteric abscess caused by a ruptured appendix. The infection spread to the regional lymphatics and along the blood vessels, forming mycotic portal emboli producing hepatic abscesses. 1, abscess of the liver; 2, infected thrombus; 3, pyelephlebitis area; 4, area of suppurative lymphadenitis with abscess; 5, appendical abscess; 6, ileum.

If nausea and vomiting are troublesome, gastric lavage combined with decompression of the stomach by means of constant suction is most helpful. Restoration of the fluid and electrolytic balances of the tissues becomes a necessity. Transfusions of whole blood not only combat existing anemias but reenforce the general immunologic defenses.

Timing of the operation requires patience, prudence and judgment. One cannot permit an overanxious family to compel one to intervene

before the process has become well localized. Many circumscribing infections have been converted into generalized peritonitis by untimely intervention. Nature is a powerful ally if given time to mobilize her defensive forces. Procrastination, on the other hand, may also bear the fruits of disappointment, for we have seen spontaneous perforations of regional abscesses result in lethal peritonitis. Progressive toxicity, persistent vomiting, acute intestinal obstruction and increasing leukocytosis are all warning signals that nature is unable to combat the infection alone and requires aid.

The choice of the anesthetic agent is very important, for complete muscular relaxation is essential in exploring and evacuating a localized abscess. Jackson<sup>11</sup> and Bower<sup>1</sup> both maintained that spinal anesthesia is ideal for this work, and we, like them, feel that it has been largely responsible for our 1.8 per cent operative mortality. It was employed for 92 per cent of all our patients ranging from 8 to 81 years of age. For the smaller children nitrogen monoxide and ether inhalations were used. The advantages of spinal anesthesia are evident, because (1) it provides complete muscular relaxation; (2) it paralyzes the intestines, so that they can be easily and safely packed away from the abscess, thus providing better visualization of the suppurative focus (fig. 4); (3) it facilitates palpatory exploration of the pericecal area by collapsing the bowels and rendering them inert; (4) if one encounters abscesses in such locations that they require drainage through several portals, this can be accomplished without resorting to time-consuming regional infiltrations, and (5) the complete muscular relaxation assures accurate apposition of the wound, thereby diminishing the incidence of post-operative hernias.

#### SHOULD THE APPENDIX BE REMOVED?

McGrath and Eiss,<sup>12</sup> Deaver,<sup>6</sup> Quain and Waldschmidt,<sup>13</sup> Ravdin<sup>14</sup> and others have expressed the sincere belief that primary appendectomy should be performed at the time the abscess is decompressed. To leave the infected organ behind is to promote wound suppuration and infections. Quain and Waldschmidt<sup>13</sup> pointed out that the morbidity rate and the resulting complications were greater with 27 appendical abscesses that were "just drained" than in 268 cases of similar involve-

11. Jackson, A. S.: Half a Million Deaths from Appendicitis, *Illinois M. J.* **76**:255, 1939.

12. McGrath, J. J., and Eiss, S.: Acute Suppurative Appendicitis, *Am. J. Surg.* **27**:112-120, 1935.

13. Quain, E. P., and Waldschmidt, R. H.: Acute Appendicitis, with Report of One Thousand Consecutive Cases, *Arch. Surg.* **16**:868-878 (April) 1928.

14. Ravdin, I. S., and Lockwood, J. S.: The Use of Sulfanilamide in the Treatment of Peritonitis Associated with Appendicitis, *Ann. Surg.* **111**:53-63, 1940.

ment in which they evacuated the pus and removed the appendix. It is only fair, however, to state that in the 27 cases in which the abscesses were merely drained the patients were considered too ill to withstand the complete operation, so the authors must have believed that simple drainage is at least the safer procedure. They maintained that ample exposure, protective packing and gentle but meticulous dissection permit the offending appendix to be safely removed. Pylephlebitis and subphrenic abscesses occur most frequently when the appendix is left in situ.

Bower,<sup>1</sup> Haggard,<sup>7</sup> Ashhurst,<sup>15</sup> Guerry<sup>3</sup> and Taylor<sup>16</sup> have stated with equal sincerity that conservative procedures should be employed. Bower<sup>1</sup> found that 50 per cent of all appendical abscesses subside spontaneously if left alone and that the other 50 per cent do much better if surgical intervention is postponed until nature's protective forces are mobilized. Guerry<sup>3</sup> treated 750 patients with primary appendical abscesses by this delayed plan, with the astoundingly low mortality of 0.8 per cent. He stated the belief that localization of the suppurative process is sufficient evidence that the patient has effectively combated the pathogens, and hence there is no urgency about the operation. If the inflammatory process is too large for its rapid absorption or if toxic reactions are evident, simple drainage affords the necessary respite for recovery. Taylor<sup>16</sup> pointed out that only 15 per cent of abscesses requiring simple drainage necessitate a secondary appendectomy.

We have neither the inclination nor the temerity to attempt to settle this controversy, for it appears that both arguments have merit. Those who practice primary appendectomy may find that their 5 per cent to 10 per cent mortality rate could be further reduced by applying conservative procedures to the "bad risk patient." Those adhering to "routine drainage" might reduce their morbidity rate by removing the offending appendix when it can be done safely. They may argue that it can never be safely accomplished, but the achievements of their contemporaries testify to the contrary. Even the most staunch advocates of primary appendectomy practice drainage when conditions dictate.

In our series of 528 cases of acute suppurative appendicitis there were 53 primary appendical abscesses, for which a primary appendectomy was performed in all but 4 cases; in these 4 the abscesses were merely drained. In 1 instance the malevolent appendix formed a primary ileocolic abscess which was so large that only drainage could be employed, but after recovery the patient refused an interval

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15. Ashhurst, A. P. C.: *Surgery: Its Principles and Practice*, ed. 3, Philadelphia, Lea & Febiger, 1927.

16. Taylor, E. H.: *Operative Surgery*, New York, William Wood & Company, 1914.

appendectomy. Six months later a second exacerbation produced another large abscess, complicated by intestinal obstruction, and again only the primary abscess could be decompressed. It required no urging, however, to convince the patient of the necessity of returning to have his troublesome appendix removed. In the 53 cases, there was but 1 operative death, which occurred on the seventh postoperative day, from delirium tremens. Autopsy revealed acute cerebral edema, terminal bronchopneumonia and a clean peritoneal cavity. This patient was chronically alcoholic, and, while one is reluctant to consider this an operative death, it only emphasizes one of the many problems which the surgeon must consider in determining the operability of a patient. No definite rule can be given, but our axiom has been to "treat each appendix as we would want some other surgeon to deal with ours." This policy makes us more hesitant to accept unnecessary risks.

#### POSTOPERATIVE THERAPY

The postoperative regimen must be carefully planned and assiduously followed if one desires a low morbidity rate. The following plan has been helpful: If spinal anesthesia has been employed, the foot of the bed is elevated for at least three hours, after which Fowler's position is assumed by the patient. Gastric decompression by means of a Levine tube is continued for forty-eight hours, thereby minimizing the postoperative ileus and the resulting gas pains. Physiologic fluids, electrolytes and vitamin concentrates are administered parenterally until the gastrointestinal tract is capable of absorbing and metabolizing these essential substances. Rest is assured by giving sufficient amounts of morphine to control the pain and to combat the nervous irritability. Hot fomentations are applied directly to the entire abdomen to relax the spastic muscles. Forced breathing and inhalations of carbon dioxide have greatly minimized the occurrence of pulmonary complications.

Sulfanilamide has proved invaluable in treating the bacterial complications of acute appendicitis, particularly if caused by the streptococcus or the staphylococcus. Since this form of chemotherapy has been used, the febrile responses, toxic reactions, wound suppuration and peritonitic infections have all been materially reduced. Whenever possible, the sulfanilamide is given by mouth, but frequently either nausea and vomiting or utilization of the Wangensteen suction tube compel us to use some other method of administration. In such instances, the drug can be added directly to the physiologic solution of sodium chloride and given subcutaneously in concentrations varying from 0.4 per cent to 0.8 per cent. This plan is particularly useful for children, as both chemotherapy and maintenance of the fluid balance can be carried out with one infusion. In some cases, however, it has been

given intramuscularly, with very pleasing results. It seems advisable to give relatively large initial doses, so that the concentration of sulfanilamide in the blood stream will reach its optimum level as soon as possible. Administration of sulfanilamide has seldom been stopped before the sixth postoperative day and has been continued for as long as three weeks in some instances. In no case were there any hemolytic or renal reactions to the drug. Absence of these complications might be explained in part by the fact that the majority of patients received one or more transfusions of whole blood to reenforce nature's immunologic reactions.

It must be remembered that actual surgical intervention is but one step in the fight; the postoperative and subsequent care are vital corollaries.

#### SUMMARY

A study is presented of 53 primary appendical abscesses which were encountered in 528 cases of acute suppurative appendicitis, an incidence of 10 per cent.

Primary appendical abscesses may be classified, according to their position, as pericecal, subhepatic, subphrenic, pelvic and ileocolic.

The anatomic, clinical and therapeutic characteristics of each type are discussed.

Primary appendical abscesses never call for emergency procedures, and time should be taken to prepare the patient properly for the surgical insult.

In fully 75 per cent of the cases the appendix can be removed safely at the time the abscess is drained. If, however, an appendectomy, either because of technical difficulties or because of the patient's condition, seems unwise, simple drainage is effective.

A secondary appendectomy should be performed as soon as the patient's condition permits.

Of 53 primary appendical abscesses, a primary appendectomy was performed for all but 4; these were merely drained. Only 1 death occurred, and this was from acute alcoholic delirium tremens. The operative mortality was 1.8 per cent. There were 2 deaths from ruptured appendical abscesses, but, as the patients were moribund from generalized peritonitis when admitted, no operation was attempted.

Sulfanilamide has proved invaluable in treating the bacterial complications of acute suppurative appendicitis. The initial dose should be large, so as to produce the optimum sulfanilamide level in the blood as soon as possible. The drug can be effectively administered by the oral, subcutaneous, intravenous or intramuscular route.

# SEVENTY-THIRD REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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## CONGENITAL DEFORMITIES

*Cervical Ribs and the Scalenus Muscle Syndrome.*—Patterson<sup>1</sup> delves into comparative anatomy to show why cervical ribs occur and to predict anatomic arrangements and into embryology to tell why certain ribs produce symptoms. He lists the anatomic types under four broad heads:

1. Enlarged transverse process, usually the seventh cervical.
2. Bilateral ribs of the floating type or articulating with the first ribs.
3. Unilateral ribs of the floating type or articulating with the first rib.
4. Rudimentary tip ribs, either single or bilateral.

He calls attention to the facts that during operation traction on the brachial plexus may produce symptoms lasting for months and that the scalenus muscle should be divided at least 1 or 2 inches (2.5 to 5 cm.) above the first rib because the pleura frequently comes up behind this

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This report of progress in orthopedic surgery is based on a review of 120 articles selected from 164 titles pertaining to orthopedic surgery and appearing in the medical literature approximately between March 1 and July 1, 1940.

1. Patterson, R. H.: Cervical Ribs and Scalenus Muscle Syndrome, *Ann. Surg.* **111**:531-545 (April) 1940.

muscle. In many cases simple division is all that is needed for relief of symptoms, but whenever there is evident pressure from a cervical rib or its tendinous attachment resection of the rib and the tendinous attachment should be carried out. He attempts to show that section of the muscle or removal of the rib may not entirely relieve the symptoms, because evidence has shown that long-continued pressure on the brachial plexus produces a chronic aseptic inflammatory reaction, which, if continued long enough, may lead to permanent fibrosis. Trauma at the time of operation may produce a similar change. Anatomic variations from the normal, such as high first ribs, bony deformities of the chest, curvatures of the spine, an enlarged scalene tubercle, variation in the origin of the brachial plexus and circulatory abnormalities may play a role in the production of symptoms in that they put increased tension on the brachial plexus.

*Cervical Ribs.*—Belgrano<sup>2</sup> made a study of 31 patients with cervical ribs and 6 with hypertrophy of the transverse process of the fourth cervical vertebra. There were 30 females and 7 males. Neurologic and vascular symptoms were found in all but 6. The most common symptoms were unilateral and bilateral pain in the shoulder and arm, muscular atrophy, paresthesia and changes in temperature and other vascular disturbances. The chief symptom of 5 was cough, and of 1, headache. There were partial paralysis of the diaphragm in 3 and paralysis of the vocal cords in 1. The arterial blood pressure was diminished on the involved side. In 21 the cervical ribs were bilateral.

*Congenital Dislocation of the Head of the Radius.*—Mauck and Butterworth<sup>3</sup> present a brief review of the literature, showing the relative rarity of congenital dislocation of the radius, and report 2 new cases. In 1 the patient was a 40 year old Negro who could not flex his elbows beyond a right angle and had limitation of pronation. He had no pain. Roentgenograms showed bilateral congenital dislocation of the head of the radius. No treatment was advised. In the second case the patient was a boy of 15 years who complained of snapping elbows, which he had always had but which were becoming worse. Examination of the elbows showed a marked increase in the carrying angles. Complete flexion and extension were possible, but there was slight restriction of pronation. On extension the heads of the radii would snap forward, but these could be reduced by flexion. Roentgenograms taken with the arms extended revealed bilateral dislocation of the head of each radius. An attempt to reduce the left radial head and hold it with a fascial sling failed, and the head was then removed. The head was found to be

2. Belgrano, M.: La costa cervicale, Gior. ven. di sc. med. **14**:155 (March) 1940.

3. Mauck, H. P., and Butterworth, R. D.: Two Cases of Bilateral Congenital Dislocation of Head of Radius, J. A. M. A. **114**:2542-2543 (June 29) 1940.



convex and small and the coronoid fossa ill formed. The right radial head was removed two weeks later. One year after the operation the patient had excellent use of both arms except for slight limitation of extension.

*Dysplastic Acetabulums and Congenital Subluxation of the Hip Joint.*—Wiberg<sup>4</sup> studied a series of so-called roentgenologically normal hips and also congenital dislocation and subluxation in both children and adults. The work was undertaken to prove whether and in what manner osteoarthritis develops from a congenital dislocation or dysplasia of the hip joint. He found that older methods of measuring the normality of hip joints were as effective as roentgen study with contrast mediums. The signs of dysplasia in children are delayed development of the epiphysial nucleus, increased width of the synchondrosis between the inferior branches of the ischium and the pubes and an increase in the inferior branches of the ischium and the pubes and an increase in the normal angle of inclination of the acetabulum. With 19 subjects he was able to compare roentgenograms taken in childhood with others taken in adult life. In 5 of these subjects maldeveloped acetabulums healed spontaneously, while 3 hips which appeared normal in childhood had maldeveloped acetabulums when the subject became an adult. Acetabular sclerosis appeared much more often in defective than in normal acetabulums. Nineteen hips which showed subluxation in roentgenograms in adult life were examined later, when osteoarthritis had developed. A definite roentgen picture was seen. This consisted of the formation of osteophytic deposits on the head in the form of a "capital drop," situated on the medial inferior section of the head, and a double acetabular floor. In a study of 257 patients with osteoarthritis of the hip the disease could be traced to subluxation in 66, or 25.7 per cent. In 15, or 59 per cent, it was due to slipping of the upper femoral epiphyses. In 13, or 5 per cent, it was due to coxa plana. In 26 it was the result of fracture or other trauma.

ED. NOTE: According to McMurray, osteoarthritis follows congenital dislocation and subluxation of the hip and Legg-Perthes disease because weight bearing through the hip joint is concentrated on a comparatively small area of the articular cartilage. There are cases of unilateral osteoarthritis of the hip joint in which no simple mechanical influence or traumatic history can be adduced. In this group the prognosis is more difficult, because the condition may develop in the unaffected hip.

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4. Wiberg, G.: Studies on Dysplastic Acetabula and Congenital Subluxation of Hip-Joint with Special Reference to Complication of Osteo-Arthritis, *Acta chir. Scandinav.* (supp. 58) **83**:1-135, 1939.

*Congenital Amputations.*—Günther<sup>5</sup> states that of two causes for congenital amputations, namely, constricting amniotic bands and endogenous malformations, the latter is the more important. In 2 cases in which siblings were examined other abnormalities of bone were discovered, although congenital amputations did not occur in the siblings.

#### DISEASES OF GROWING AND ADULT BONE

*Parathyroid Function and Osseous Disease.*—Helflet<sup>6</sup> questions the generally accepted view that the function of the parathyroid glands is the control of the calcium level in the blood.

He puts forward the theory that parathyroid extract exerts its primary effect on the phosphorus metabolism and effects its control (1) by stimulating excretion of phosphate by the kidney and (2) by mobilizing calcium ions from the bone, thus forming inactive calcium phosphate. The evidence in favor of this view is carefully listed and examined.

An account is given (with case reports) of the results of treatment of hyperparathyroidism, tetany, Paget's disease and rheumatoid arthritis. An aluminum salt was used to decrease the phosphate intake.

ED. NOTE: Hypertrophy of the parathyroid glands has been produced experimentally with low calcium diets, and hypoplasia of the parathyroid glands has been produced by injection of calcium gluconate. Ham and others recently showed that hypocalcemia, instead of hyperphosphatemia, is the primary cause of physiologic hypertrophy of the parathyroid glands.

It would seem that Helflet's reduction in the phosphate intake may have acted through a relative increase in the ionized calcium in the blood. Other workers have contributed considerable evidence which would indicate that Helflet's assumptions may not be correct.

*Osteitis Deformans.*—Sugarbaker<sup>7</sup> reviews 51 cases of Paget's disease from the records of the Henry Ford Hospital in Detroit, together with extracts from the literature. The age at which the disease was recognized in this series was from 40 to 77 years, the average being about 58. The chief symptom is pain, which is usually in the back and legs and is probably due to periosteal and ligamentous stretching. The osseous changes are seen most frequently in the skull, spine, pelvis, femur and tibia, in this order. In 24 per cent of the cases the condition

5. Günther, R.: Zur Frage der angeborenen Amputationen, Ztschr. f. menschl. Vererb- u. Konstitutionslehre **23**:736-768, 1939.

6. Helflet, A. J.: New Conception of Parathyroid Function and Its Clinical Application: Preliminary Report on Results of Treatment of Generalized Fibrocystic and Allied Bone Diseases and of Rheumatoid Arthritis by Aluminum Acetate, Brit. J. Surg. **27**:651-677 (April) 1940.

7. Sugarbaker, E. D.: Osteitis Deformans (Paget's Disease of Bone): Review of Fifty-One Cases, Am. J. Surg. **48**:414-421 (May) 1940.

was monostotic, an unusually high incidence. The roentgen findings consist of a heterogeneous confluence of areas of osteoporosis and osteosclerosis, the former predominating in the early stages and the latter in the advanced stages, with a tendency toward overgrowth and thickening of the bone. Chemical studies show that the calcium and phosphorus content of the blood is normal, while the phosphatase content shows an increase roughly proportional to the extent of osseous involvement. The average value for phosphatase in this series was 12.74 Bodansky units. In regard to complications, deafness and optic atrophy may result from foraminal compression. Fractures occur in about 15 per cent of cases, but healing takes place promptly. Urinary calculi may occur. Sarcomatous degeneration has been reported in from 2 per cent to 9.5 per cent of the cases. This change probably occurs about ten to fifteen years after the onset of the disease and is apt to be highly malignant. Treatment is, in general, symptomatic. Roentgen therapy may mitigate the pain. Diets rich in calcium and vitamin D have been used, as have high magnesium diets. More recently extracts of adrenal cortex have been employed, with encouraging results.

*Generalized Epiphysiolysis.*—Müller<sup>8</sup> reports the autopsy observations in the case of a 16 year old boy with generalized epiphysiolysis. In addition to the disturbances in the epiphyses, a basophil adenoma of the hypophysis, hyperplasia of all parathyroid glands and arteritis obliterans were noted.

*Epiphysial Dysplasia Puncticularis.*—McCullough and Sutherland<sup>9</sup> report a case of epiphysial dysplasia puncticularis in a boy of 9 years. The child showed no evidence of hypothyroidism. He was brought to the clinic because of shortness of stature. Roentgenograms of the skeleton showed "the general osseous development to be normal for the age of the patient, except that the bones were shorter than usual. The capital epiphyses of the humeri and femora and epiphyses for the greater trochanters showed marked fragmentation in the form of coarse, granular stippling with some irregularity and trumpeting along the metaphyseal borders, entirely dissimilar in its appearance to rickets. The epiphyses of the elbow joints and the wrists showed a mild degree of these changes, but the stippling occurred only in the epiphyses of the olecranon processes. . . . There was a marked epiphysitis of the entire spinal column."

8. Müller, W.: Generalisierte Epiphyseolysis adolescentium und doppelseitige Fälle von Coxa vara adolescentium, Arch. f. orthop. u. Unfall-Chir. 40:1-13, 1939.

9. McCullough, J. A. L., and Sutherland, C. G.: Epiphysial Dysplasia Puncticularis (Stippled Epiphyses): Report of Case Not Associated with Hypothyroidism, Radiology 34:131-135 (Feb.) 1940.

This condition has been described rather uncommonly in association with hypothyroidism. In this case there were no signs of hypothyroidism.

ED. NOTE: Harris states that the fundamental disturbance in cases of "stippled epiphysis" is identical with that in cases of achondroplasia. There was a fundamental deficiency in the cartilage. Mucoid degeneration of the epiphyses is noted.

*Changes in Long Bones of Newborn Infants After Administration of Bismuth Preparations.*—Whitridge<sup>10</sup> gave weekly injections of 1 cc. of bismuth salicylate in oil to 12 nonsyphilitic women during the last trimester of pregnancy and by means of roentgen examination of the children during their first week of life was able to prove Caffey's assumption that the changes which appear in the bones of infants of syphilitic mothers are produced by bismuth and not by healed syphilitic osteochondritis.

Nine of the 12 infants showed changes, which consisted of transverse bands of increased density near the ends of the long bones, but apparently these alterations were independent of the total amount of bismuth given. One of these infants died on the second day of life, after a difficult breech delivery, and postmortem roentgen examination of the skeleton showed well defined bands of increased density. Autopsy revealed intracranial and intra-abdominal hemorrhages. Microscopic sections of the upper end of the tibia and of the lower end of the femur showed an excessive amount of calcified matrix substance which extended down into the shaft as a dense zone for about 1 mm. The trabeculae of calcified matrix were for the most part devoid of bone. There was no excess of osteoclasts, such as is seen in cases of lead poisoning. A chemical test for bismuth in portions of these bones gave negative results.

#### PYOGENIC INFECTIONS OF BONES AND JOINTS

*Acute Hematogenous Osteomyelitis.*—McCoy and Ross<sup>11</sup> maintain that acute osteomyelitis can be divided into two main types, depending on whether the blood culture is positive or negative. The positive group may be subdivided according to whether there are more or fewer than 10 bacterial colonies per cubic centimeter of blood.

The authors found that surgical drainage is essential and is indicated even in the presence of severe septicemia. This drainage is best done by the Orr method. The rise in the mortality rate is proportional to the severity of the septicemia. Recovery occurred in their cases in

10. Whitridge, J., Jr.: Changes in the Long Bones of Newborn Infants Following the Administration of Bismuth During Pregnancy, *Am. J. Syph., Gonorr. & Ven. Dis.* 24:223-227 (March) 1940.

11. McCoy, R. H., and Ross, D. E.: Acute Hematogenous Osteomyelitis, *Canad. M. A. J.* 42:162-168 (Feb.) 1940.

which the blood showed not more than 10 colonies per cubic centimeter. On the other hand, only 1 patient recovered when there were more than 10 colonies per cubic centimeter.

The best method of administering a staphylococcic vaccine is by continuous intravenous drip, but the authors feel that this mode of treatment is of little value in any case, although it tends to decrease the number of bacterial colonies in the blood cultures.

*Infection of Bone in Newborn.*—Cass<sup>12</sup> reports 3 cases which support the statements of Green and of Dillehunt that osteomyelitis of the long bones in infants is locally relatively benign and also show that uncomplicated staphylococcic osteomyelitis in the newborn is associated with virtually no systemic disturbance.

Advice was sought because of the swelling, as there was no pain unless the infected bones were moved. The patients slept and behaved normally and took their feedings well. Occasionally they had loose stools, but no serious gastrointestinal disturbances were noted. Pyrexia was slight in view of the suppuration present, and, accordingly, conservative treatment was adopted. The babies did not lose weight or appear wasted at any time during treatment. Moderate anemia developed in all 3 of the author's cases. In a purely staphylococcic infection there is no infection of the lungs, peritoneum, meninges or skin, and the prognosis, apart from the risk of deformity, is good.

Evidently there is no urgency for operative treatment. When the epiphysial line is intracapsular there is a marked tendency to early involvement of the joint because of the rapid escape of pus through the cortex, but little disability or deformity results. The only permanent deformities in 2 of the 3 cases reported were due to erosion and shortening of the articular ends of the bones and to adhesions in the joints. Deformities in 1 case followed incision of an abscess, and in the other they followed repeated aspiration of the pus. The advantage of repeated aspiration rather than open drainage is the avoidance of the risk of secondary infection of the wound.

It is not clear from the reported cases whether the prognosis is equally good for osteomyelitis in infants when the infection is due to organisms other than the staphylococcus.

*Suppuration of Knee Joint.*—Maurer<sup>13</sup> divides infections of the knee into empyema of the joint, phlegmon of the capsule and para-articular or extra-articular infection. He advises treating empyema of the joint with rest in slight flexion in a cast, frequent needling or drainage through

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12. Cass, J. M.: Staphylococcus Aureus Infection of Long Bones in Newly Born, Arch. Dis. Childhood **15**:55-60 (March) 1940.

13. Maurer, G.: Die Kniegelenkeiterung, Arch. f. klin. Chir. **197**:639-647, 1940.

anterior and posterior incisions and washing with a phenol-camphor solution. For phlegmon of the capsule the joint is put at rest by a plaster cast which includes the ankle and hip. If drainage through posterior and anterolateral incisions does not result in improvement, better drainage is obtained by opening the whole knee by a horseshoe incision. Occasionally, amputation is necessary to save life. In 26 cases of phlegmon of the capsule the end results were 14 stiff knees, 3 with slight motion; 4 amputations; 4 deaths, and 1 unknown result. For para-articular infections incision and drainage are usually sufficient.

ED. NOTE: The author's terminology and apparently his treatment of infections about the knee joint are not in complete accord with those generally accepted in the United States.

*Acute Infectious Lesions of the Intervertebral Disks.*—Ghormley, Bickel and Dickson<sup>14</sup> call attention to a destructive lesion of the intervertebral disk on an infectious basis, either primary or secondary. The onset is sudden and is associated with a more or less severe febrile reaction. This lesion has previously been recognized but is usually designated as osteomyelitis of the vertebrae. It presents the same difficulties of diagnosis in its early phases as does acute osteomyelitis of the vertebrae. There is a marked difference in the pathologic characteristics, course and prognosis between this lesion of the disk and acute osteomyelitis of the vertebrae. Abscess formation was not encountered in these cases. Twenty cases were observed at the Mayo Clinic. The average duration of the acute symptoms in the back was twenty-one and six-tenths weeks; the shortest duration was six weeks, and the longest, two years. The roentgenogram presents the most important feature of these cases. In the early stages there may be thickening of the paravertebral soft parts. As one follows the lesion in the roentgenograms, there are seen progressive thinning of the disk with osteophyte formation at the margins of the involved vertebrae and even bony fusion of the adjacent vertebral bodies.

ED. NOTE: Many of these lesions are seen long after the acute phase. This lesion demonstrates the importance of a careful and detailed past history in the differential diagnosis of lesions involving the intervertebral disk. Many surgeons have seen this lesion but have designated it as a result of osteomyelitis. In many cases osteomyelitis of the spine has been diagnosed as tuberculosis until the past history has been taken into account.

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14. Ghormley, R. K.; Bickel, W. H., and Dickson, D. D.: Study of Acute Infectious Lesions of Intervertebral Disks, *South. M. J.* **33**:347-353 (April) 1940.

## CHRONIC ARTHRITIS

*Foreign Body Arthritis.*—Key<sup>15</sup> reports 6 cases in which a foreign body entered a joint and remained there for a considerable time, producing arthritis in the joint. Roentgenograms and case histories are given. He concludes that a foreign body in or near a joint cavity may serve to prolong and keep active a mild, low grade infection and may result in destruction of the joint. Even though infection is not present, he finds that if the foreign body is allowed to remain in or near the joint cavity severe progressive degenerative arthritis may result. Therefore, foreign bodies in or near joints should be removed early. In 1 case, in which a bullet entered the intervertebral disk and caused its destruction, fusion of the adjacent two vertebral bodies resulted and no further symptoms were noted. One might conclude from this single incident that when vertebral fusion results the foreign body need not be removed.

*Diagnosis of Neuropathic Joint Disease (Charcot Joint).*—Soto-Hall and Haldeman<sup>16</sup> present an analysis of 40 cases. Thirty of the patients were males and 10 were females. A comparison of sex incidence in this series with observations (by Poole) of the preponderance of male tabetic patients indicates an equal susceptibility in the two sexes to involvement of the joint once the underlying disease is present. Tabes dorsalis, though the most frequent underlying disease, is not the only condition which may lead to the development of neuroarthropathy. A similar loss of sensibility in the joint may occur in the presence of syringomyelia, injury to the spinal cord or leprosy. The joint becomes swollen and relaxed and the articular cartilages thinned; marginal fractures occur; sclerosis of subchondral bone may occur in some areas and atrophy in others; loose bodies arise in the joint, and new bone formation takes place outside the joint cavity. Many of these features can be demonstrated by roentgen examination. The absence of pain is the most striking clinical observation. In 18 of 40 cases severe trauma was the initiating factor. The tendency to bilateral involvement was seen in 16 cases in which two or more joints were affected. The positive clinical evidence of rigid pupils and absent knee jerks is of much greater importance in the diagnosis of tabetic arthropathy than are the various tests performed on the blood and spinal fluid. Microscopic sections from 8 joints were studied. A culture of the synovial fluid should be made prior to any operation on a Charcot joint, since pyogenic organisms may be present.

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15. Key, J. A.: Foreign Body Arthritis, Surg., Gynec. & Obst. **70**:897-902 (May) 1940.

16. Soto-Hall, R., and Haldeman, K. O.: The Diagnosis of Neuropathic Joint Disease (Charcot Joint): Analysis of Forty Cases, J. A. M. A. **114**:2076-2078 (May 25) 1940.

*Spondylitis Ankylopoietica*.—Buchmann,<sup>17</sup> in a study of 200 patients with ankylosing spondylitis, found that most of them were youths and men between 18 and 25 years of age. Many had been athletes. He found changes in the sacroiliac joints before symptoms appeared in the back. These changes were a regional decalcification, a widening of the fissure of the joint, a blurring of the articular contour and small, round, clear areas. The symptoms come on at first intermittently, gradually localizing low in the back. With this condition there are sleeplessness, loss of weight, anemia, an increased sedimentation rate and, occasionally, fever. Iritis is observed in about 10 per cent of the patients. The author advises wide field roentgen therapy.

*Arthritis and Para-Arthritis Treated with Roentgen Ray*.—Weinberg<sup>18</sup> reports 161 cases of arthritis and para-arthritis treated with roentgen irradiation. The series included cases of arthritis, mainly of the hypertrophic variety; cases of bursitis, in the large majority of which the condition was subdeltoid and subacromial, and cases of spondylitis involving the cervical, dorsal and lumbar portions of the spine. Some conditions were diagnosed as neuritis, whereas others were labeled "algias," such as metatarsalgia or neuralgia. Still others were called rheumatism. Pain was the predominant symptom. The most frequently demonstrable pathologic observation was a deposit of calcium in the region of the affected joint. The deposit was either outside the joint, as seen in cases of bursitis, or visualizable within the joint, as in cases of osteoarthritis. The treatment was given directly over the involved area. The dose was 100 to 150 r two or three times weekly, and from three to twelve treatments were given. It was found that the shorter the duration of the symptoms the sooner the condition was alleviated and that the more chronic the involvement the longer the period required to bring about satisfactory results. The large majority of the patients were completely relieved of pain and remained free from symptoms. Several had one or more recurrences and were relieved by a repeated course of treatments. A few did not respond to this form of therapy.

ED. NOTE: In a recent review of the problem of rheumatism and arthritis, Hench and others found that opinions differ as to the value of roentgen therapy for chronic arthritis. It seems to be of some value in selected cases, particularly those in which there is periarticular inflammation.

17. Buchmann, E.: Spondylitis ankylopoietica, Nord. med. (Norsk mag. f. lægevidensk.) 5:12-20 (Jan. 6) 1940.

18. Weinberg, T. B.: Arthritis and Para-Arthritis Treated with the Roentgen Ray: Report of One Hundred and Sixty-One Cases, Am. J. Roentgenol. 43: 416-424 (March) 1940.



*Treatment of Arthritis with Sulfur.*—Abrams and Bauer<sup>19</sup> have taken issue with the old statement that in persons with rheumatoid arthritis there is a sulfur deficiency. They have treated 14 patients with colloidal sulfur. The average dose was about 350 mg. However, 1 patient stopped treatment after taking 160 mg. Three received massive doses, the largest being 2,980 mg. The results are recorded separately under subjective, objective laboratory evidence of improvement, the final impression being gathered from an analysis of all three. The results closely correspond to those obtained by Freyberg, Black and Fromer, who, in experimental work, found that there was no fundamental difference in the amount of sulfur excreted or in the manner in which it is excreted by arthritic and by control subjects and also that injected sulfur is eliminated chiefly as inorganic sulfate, there being no increase in the conjugation of sulfur. Analysis of the finger nails shows no change in the cystine content before and after sulfur medication. Response does not vary with the amount of sulfur given. Even very large doses, up to 100 mg. at a time, are no more efficacious than smaller ones.

*Joint Analgesia.*—Coronedi<sup>20</sup> reports on the treatment of stiffness in joints in 29 cases by local infiltration of procaine hydrochloride. The stiffness was due to long immobilization for fracture, trauma and especially gonorrheal arthritis. An 8 per cent solution was used, in amounts of about 6 cc. The analgesia appeared in one-half hour and lasted for several days. The anesthetic was as effective in the periarticular tissues as when it was injected into the joint also. With more serious disturbances of function, repeated injections at long intervals combined with physical therapy gave good results in the majority of cases. The treatment failed in the presence of gross anatomic changes, such as destruction of the cartilages or bony ankylosis.

#### MUSCULAR AND NEUROMUSCULAR DISORDERS

*Myositis Ossificans Traumatica.*—Thorndike<sup>21</sup> expresses the belief that with true myositis ossificans signs of muscle inflammation develop early and that as ossification takes place the inflammation subsides, disappearing when the muscle function returns to normal. The pathologic sequence of events is: (1) severe deep muscle contusion, accompanied with the tearing of muscle fibers and capillaries and the loosening

19. Abrams, N. R., and Bauer, W.: Treatment of Rheumatoid Arthritis with Sulfur: Critical Evaluation, New England J. Med. **222**:541-546 (March 28) 1940.

20. Coronedi, L. B.: Recenti acquisizioni relative all'analgnesia articolare nel campo della ortopedia, Arch. di ortop. **55**:473-504 (Dec. 31) 1939.

21. Thorndike, A., Jr.: Myositis Ossificans Traumatica, J. Bone & Joint Surg. **22**:315-322 (April) 1940.

of periosteal cells; (2) hemorrhage, with the accompanying inflammatory reaction that one would expect with hematoma formation, and (3) hematoma absorption, in which stage ossification takes place.

Absorption of the ossification occurred in 9, or 36 per cent of the author's series of 25 cases. In 1 case, of severe involvement, only partial absorption occurred in five years. Absorption depends on size and location of the process as well as on the individual diathesis.

The femur was the most frequent site of involvement in the author's series (51.9 per cent).

The diagnosis is clearcut. For example, if a muscle contusion is treated with diathermy and in the course of four or five days after injury does not seem to respond properly but becomes tenderer, firmer and warmer and loses function daily, it may be assumed that myositis ossificans is developing. The muscle becomes sensitive even to ordinary light massage. In such a case all such treatment should be stopped, and rest, heat and elevation should be instituted. The ossification per se does not become discernible by means of roentgen rays until between the sixteenth and the twenty-first day. Heat should be applied daily and regularly until normal muscle function is restored.

Prevention of such diseases consists of (1) protection from injury; (2) immediate institution of measures to control hemorrhage, i. e., application of cold for one hour and the use of a compression bandage with sponge rubber, and (3) omission of massage.

Operation is contraindicated if the ossification is in the belly of a muscle or on the shaft of a bone. If it is indicated, it should not be done until twelve to twenty-four months after the injury.

ED. NOTE: The author's findings correspond to those of one of the editors, who has had a broad experience in the treatment of athletic injuries.

*Muscular Atrophy and Weakness in Thyrotoxicosis.*—Morgan and Williams<sup>22</sup> report 4 cases of marked generalized myopathies and asthenia developing in patients with thyrotoxicosis. Weakness was the first sign and appeared in the arms, hands, legs, back or throat. There were muscle atrophy, muscular twitchings and loss of weight. The muscle weakness overshadowed and usually preceded the signs of thyrotoxicosis. The deep reflexes were usually hyperactive or normal. Babinski's sign was absent. No objective sensory disturbance or abnormality of the cranial nerves was noted. The writers review 4 other cases from the literature. The results of thyroidectomy were striking. The patients gained weight and strength rapidly, and in a few months 6 of them

22. Morgan, H. J., and Williams, R. H.: *Muscular Atrophy and Weakness in Thyrotoxicosis: Thyrotoxic Myopathy; Exophthalmic Ophthalmoplegia*, South. M. J. 33:261-269 (March) 1940.

experienced complete restoration of health without evidence of residual damage to muscle. The result in 1 case was observed too soon after operation to evaluate. One patient died before operation, owing to failure of the muscles of respiration. One showed generalized demineralization, with fracture of two vertebrae. This was the patient whose case was observed too early to evaluate the result. The writers add a case of exophthalmic ophthalmoplegia developing fourteen months after thyroidectomy, when the basal metabolic rate was in the minus zone.

The writers cite the work of Askanazy, who showed areas of degeneration and fatty infiltration in muscles of patients who died of hyperthyroidism, and that of Dudgeon and Wiquhart, who found lesions characterized by the accumulation of lymphocytes in the muscles of such patients. The authors performed biopsies of the muscles; in 1 case the muscle showed a normal structure, and in another case there was some atrophy of muscle fibers.

*Vitamin B<sub>6</sub> for Pseudohypertrophic Muscular Dystrophy.*—Antopol and Schotland<sup>23</sup> report 6 cases of pseudohypertrophic muscular dystrophy treated with synthetic vitamin B<sub>6</sub>. Since the vitamin is a newly synthesized compound, its pharmacologic action has not been sufficiently investigated, and its effects can be accounted for only theoretically. The finding of muscle atrophy in rats deficient in vitamin B<sub>6</sub> and the production of tremors and convulsions in rats after the administration of massive doses of synthetic vitamin B<sub>6</sub> indicate that this vitamin may have some effect on muscle action. All of the 6 children treated with the vitamin showed considerable improvement. One patient had a relapse and, despite intensive therapy, became worse. No untoward symptoms were observed from this form of treatment.

*Vitamin E for Muscular Dystrophies and Allied Conditions.*—Stone<sup>24</sup> presents a preliminary report on the use of vitamin E (wheat germ oil) in the diet of a number of patients with muscular dystrophy and muscle atrophy. The group included 13 children with muscular dystrophies, 1 child with muscular atrophy following anterior poliomyelitis and 1 patient with advanced muscular atrophy coming on after an attack of neuromyeloradiculitis. In 7 cases the treatment had progressed long enough to permit definite conclusions as to results, and each of these is presented in some detail. The treatment consisted of giving about 2 cc. of wheat germ oil daily, together with an ample supply of vitamin B complex, and an increase in amino acid intake through daily feedings of gelatin. The medication is usually well

23. Antopol, W., and Schotland, C. E.: Use of Vitamin B<sub>6</sub> in Pseudohypertrophic Muscular Dystrophy, *J. A. M. A.* **114**:1058-1059 (March 23) 1940.

24. Stone, S.: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on Use of Vitamin E (Wheat Germ Oil), *J. A. M. A.* **114**: 2187-2191 (June 1) 1940.

tolerated by all patients. The response to treatment is usually prompt, consisting in (1) improvement in appetite, (2) disappearance of pain on exertion, (3) greater resistance to fatigue and (4) replacement of rubbery muscles by normal muscle tissue. These changes were observed in 5 cases of muscular dystrophy. In 2 cases of muscular atrophy an increase in regeneration of muscle tissue became apparent.

ED. NOTE: The exact part played by vitamin E in the process of proteolysis and its influence on muscle metabolism have not been fully determined, and further clinical investigation is needed. It has been shown experimentally by Knowlton, Hines and Brinkhous that adult rats reared from birth or from weaning on a vitamin E-deficient diet eventually have muscular dystrophy, and it was found that subcutaneous injections of synthetic alpha tocopherol are effective in both the cure and the prevention of nutritional muscular dystrophy in rats. On the other hand, there is some evidence that vitamin E may be carcinogenic. Unna and Antopol found that doses of not more than 1 Gm. per Kg. of body weight vitamin B<sub>6</sub> produced tonic convulsions in rats and that the lethal dose produced death in thirty-six to seventy-two hours. Accordingly, it is evident that these substances should be used with caution and that additional experimental work is needed.

*Paralysis of the Serratus Magnus Muscle.*—Overpeck and Ghormley<sup>25</sup> report a group of cases of paralysis of the serratus magnus muscle. The most prominent symptom of isolated paralysis of the long thoracic nerve and the serratus magnus muscle is pain. Trauma to muscle produces a more severe type of pain than that associated with involvement of the nerve only. The second most common symptom is fatigue on elevating the arm or inability to elevate the arm fully. A third symptom is abnormal prominence of the scapula. The principal clinical observations are weakness of pushing power of the affected shoulder and weakness of abducting power above the horizontal plane. Winging of the scapula is always present when the arm is fully abducted or is elevated anteriorly. Trauma was the chief causative agent in 23 of the 28 cases studied. Trauma was classified into three types: (1) acute, (2) recurrent irritative and (3) contributive. In 15 of the 28 cases it was of type 1. In 1 case the paralysis occurred after the patient made a vigorous swing at a punching bag and missed it. A horse kicked 1 patient in the axilla. Under type 2 there were 7 cases. In 1 instance the lesion resulted after the patient, a carpenter, had carried boards on his shoulder over a period of three years. In 1 case the trauma was classified as type 3. In the history of the patient there was a definite

25. Overpeck, D. O., and Ghormley, R. K.: Paralysis of Serratus Magnus Muscle Caused by Lesions of Long Thoracic Nerve, J. A. M. A. **114**:1994-1996 (May 18) 1940.

relation of trauma to strenuous work and exposure to bad weather. Another causative agent was infection. Both operative and conservative forms of treatment are discussed. Physical therapy and support of the extremity are the most universally successful methods, and the prognosis for restoration of function is good in the majority of instances.

ED. NOTE: A similar case, observed by one of the editors, was that of a patient who had had no pain and who accidentally discovered the condition. There was no history of trauma other than the excessive driving of an automobile with the affected arm elevated on the window sill. There was no history of infection, with the exception of a "severe cold" which the patient had contracted a few weeks before the deformity was noted.

#### FRACTURES AND DISLOCATIONS

*Colles' Fracture.*—Mayer<sup>26</sup> points out that various recent reports of end results of Colles' fracture indicate that 15 per cent to 20 per cent are imperfect.

He considers that this is largely due to failure to recognize that part of the displacement present is commonly a supination twist of the lower fragment on the upper and consequent failure to splint the limb in such a way that pronation of the lower fragments is maintained. The author effects this by means of a skin-tight plaster carried above the elbows.

Experimental fractures were carried out on dissecting room subjects to demonstrate the mechanism causing this supination displacement.

*Fractures of the Tarsal Scaphoid Bone.*—Lance<sup>27</sup> states that the scaphoid bone represents the true center of movement of the foot. It transmits pressure from the leg and the posterior part of the foot to the cuneiform metatarsal region and gives elasticity to the gait. The astragalus exerts its maximum pressure on the center of the scaphoid bone, which is also its weakest portion. A fracture of the scaphoid is usually caused by a fall from a height, the distal end of the foot being struck on the ground. It is rarely due to a twist of the foot without a fall. The bone is most commonly broken into two or three fragments. The displacement of the fragments is determined by the displacement of the astragalus and by the resistance of the astragaloscaphoid and the scaphocuneiform ligaments. Most frequently the scaphocuneiform ligaments hold and the head of the astragalus crushes the scaphoid fragments forward and laterally. The articular facets of the fragments lose contact with the astragalus but maintain their contact with the cuneiform ligaments. Partial midtarsal dislocation results. If the scaphocuneiform ligaments rupture, the superior fragment is expelled toward the skin, simulating a dislocation of the scaphoid bone.

26. Mayer, J. H.: Colles's Fracture, *Brit. J. Surg.* **27**:629-642 (April) 1940.

27. Lance, P.: Le traitement des fractures du scaphoïde tarsien, *J. de chir.* **54**:625-642 (Dec.) 1939.

Untreated fractures of the scaphoid bone result in painful valgus and partially ankylosed flat foot. The head of the astragalus, no longer maintained by the scaphoid, sags downward and inward. Mechanical arthritis develops in Chopart's joint. Loss of mobility results in mid-tarsal, in the subastragular and even in the anterior joints of the foot.

In regard to treatment, fractures without displacement may be placed in a plaster cast in a little varus, with a well molded arch, for three weeks. If there is displacement of the fragments, the foot is flexed and abducted to open the scaphoid space, and the fragments are molded into place. The foot is then placed in the varus position in plaster for six weeks. It is often difficult to reduce the fracture or to maintain reduction by this method; subluxation of the head of the astragalus may persist. Surgical treatment should be employed only after failure of the aforementioned procedure. In a few cases the bone can be replaced surgically, but it is difficult to do this, and it is also hard to hold the reduction. Hence, one of the fragments or the entire bone is usually removed, with or without astragalocuneiform fusion. One fragment should be removed only if the remaining fragment is large enough to insure astragalar stability. Complete scaphoidectomy is not a good procedure because of subsequent varus deformity and instability of the foot. Resection of the bone followed by astragalocuneiform arthrodesis or complete midtarsal fusion is a worth while operation. Occasionally, subastragalar fusion is indicated.

*Compound Fractures.*—Heyl<sup>28</sup> discusses the treatment and results of compound fractures of the long bones observed in 128 patients during a twelve year period at the Beekman Street Hospital in New York. Traction was usually applied to the injured extremity before the patient reached the hospital, and it was kept applied until the fracture could be more adequately treated. The immediate treatment on admission consisted in the administration of tetanus antitoxin and the application of a tourniquet if bleeding from the wound was severe. The tourniquet was loosened every twenty minutes but reapplied. The usual treatment for shock, if this was present or seemed likely to supervene, was given. The patient's general condition and the possibility of complicating injuries were carefully considered.

Débridement of the wound was delayed until the surgeon felt that the patient's condition was satisfactory. The delay at times was as long as twelve hours, and during this period the tourniquet was left in place.

The "clean-up" and débridement are described in detail. The author is strongly opposed to closure of the wound and is definitely against leaving suture and other foreign material within it. If infection seemed

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28. Heyl, J. H.: The Treatment of Compound Fractures of the Long Bones, *Ann. Surg.* **111**:470-490 (March) 1940.

likely, Dakin tubes were introduced at the time of the débridement. If débridement was not performed within six hours of the injury, it was usually omitted.

There were 26 deaths, 13 occurring within the first thirty-six hours after admission. Sixteen patients were subjected to amputations. Infection occurred in 48 per cent of the cases in which a lower extremity was involved and in 41 per cent of those in which an upper extremity was involved. The Orr treatment was advocated in cases in which an infection developed.

ED. NOTE: The author does not discuss prophylactic doses of anti-toxin for gas gangrene or the use of roentgen therapy for this condition.

The use of hemostats (where possible) or of a compression bandage would seem to be less detrimental than the prolonged use of a tourniquet proximal to tissues which are already partially devitalized. The use of the tourniquet may be a factor in prolonging the shock.

In most cases which are not complicated by extensive injury elsewhere the shock is readily and quickly relieved by traction on the extremity and by the other methods by which it is combated. It will often be found beneficial to proceed with the débridement as soon as the patient has begun to respond.

Contrary to the findings of the author, there are clinics where early, thorough débridement and closure of the wound are usually performed and are associated with virtually no infections and a relatively low mortality rate.

Some surgeons have found the use of vitallium plates combined with the Orr method of treating infected wounds to be entirely satisfactory.

The use of drains in cases of peritoneal abscesses is hardly comparable to their use for compound fractures, as was suggested by the author.

*Treatment of War Fractures.*—Soulié and Linares<sup>29</sup> applied the method of treatment known as "late closed healing" to 389 wounded soldiers at a temporary hospital. The majority had large wounds with compound fractures and with foci of osteomyelitis. Some were very toxic old fractures with suppuration of long duration. The treatment, in brief, consisted of: débridement and saucerization of the wound; extraction of foreign bodies and detached pieces of bone; reduction of the fracture, and application of a plaster cast without dressings, padding or windows. The authors feel very strongly that complete rest will heal wounds, while daily dressings will infect them. Attempts at chemical sterilization of wounds are futile. A distinction is drawn between

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29. Soulié, J., and Linares, C.: La cure occlusive dans le traitement des fractures de guerre, *J. de chir.* 55:22-37 (Jan.) 1940.

the treatment of fresh wounds in civil practice and in war practice. In civil practice a fresh wound which can be débrided within the first six hours should usually be closed, while a war wound even in this early period, after débridement and saucerization should be left largely open. The plaster cast should be applied directly to the skin and to the wound without dressing or padding. This permits drainage to occur between the inner surface of the plaster and the skin, and the exudation is partly absorbed. Contraindications to this treatment are: (1) vascular lesions; (2) gas gangrene; (3) conditions in which complete excision of contaminated tissue cannot be done and the wound cannot be saucerized, and (4) fractures requiring continuous extension. In the presence of any of these conditions the wounds are usually left completely bare.

ED. NOTE: Compound fractures are being treated by Orr's method in many clinics. Some orthopedists maintain that fixing the fragments with a vitallium plate before application of a cast is beneficial rather than detrimental. We do not see the advantage of application of the cast to the wound without dressings.

*Old Ununited Intracapsular Fractures of the Neck of the Femur.*—Compere and Lee<sup>30</sup> review the historical development of the present method of treating ununited fractures of the neck of the femur. Clearly drawn descriptive sketches depict each procedure. These include: 1. The methods of Whitman, Colonna, Albee and Campbell, who remove the femoral head. 2. The methods of Brackett and the high and low osteotomies of Schanz, both of whom leave the femoral head in place. 3. The methods of Albee, Campbell and Henderson, in which a bone graft plus plaster cast fixation is used; the method of Ellis Jones, which is similar to that just described except that he takes his bone graft from the greater trochanter; the method of Dickson, in which bone chips plus a Smith-Petersen nail are utilized, and, finally, the authors' method, which consists of placing two bone grafts in the neck of the femur with threaded wire fixation.

During the years 1934 to 1936 two tibial bone grafts were used successfully in 3 cases, but painful, limited motion of the knee resulted because plaster spicas had been used. Recently, to lessen the period of hospitalization and the dangers of immobilization, threaded 18-8 stainless steel wires, gage 0.080, with 56 threads to the inch, were used effectively to obtain immobilization and union.

Their technic is as follows: With the patient under general anesthesia, traction is applied on the operating fracture table. A modified Smith-Petersen approach is used. After the fracture line has been exposed, traction is increased until a valgus position between the neck

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30. Compere, E. L., and Lee, J.: Restoration of Physiological and Anatomical Function in Old Ununited Intracapsular Fractures, *J. Bone & Joint Surg.* 22: 261-277 (April) 1940.



of the femur and the shaft is obtained. Fibrous union was disturbed only to obtain alinement of the fragments and approximation of the fracture surfaces. Two drill holes  $\frac{1}{2}$  inch (1.2 cm.) in diameter are made through the greater trochanter, through the femoral neck and across the fracture site into the head of the femur. Into each of these a tibial bone graft is driven. Three or more threaded wires are drilled in as described by Moore.

The authors found that the wires removed nine months to two years afterward were still holding and had to be unscrewed. Seven cases are reported, including 1 of failure resulting from a technical error. Under this method the period of hospitalization was reduced to an average of only twenty-four days. The patients were in wheel chairs in about a week and ambulatory with crutches in two to three weeks. Weight bearing is not permitted for five months or longer, but early active and passive exercises are encouraged.

Excellent illustrations, specimen photographs and roentgenograms accompany the text. A table summarizing the results of all the cases reported speaks for itself in favor of this method of treating these difficult fractures.

*Treatment of Sprains and Dislocations of the Knee.*—Leriche<sup>31</sup> expresses the belief that the characteristic clinical picture of sprain (edema, local heat, pain and loss of function) arises from functional circulatory phenomena. This picture can and often does exist without macroscopic lesions. Ligamentous rupture and bony lesions are complementary states aggravating the prognosis but not essentially changing the symptoms. Differentiation of these lesions is made by immediate infiltration of procaine hydrochloride, followed by careful palpation and testing of abnormal motion with, finally, roentgen examination. In regard to treatment, if there is no rupture of the ligaments the region of sprain is infiltrated with procaine hydrochloride, and the patient resumes walking immediately. A second injection is given the following day if necessary. If the ligaments are torn, immobilization (in the case of an ankle) is carried out for fifteen days. If a bony fragment is avulsed, a small incision is made and the fragment is either removed or fastened in place.

In case of sprains of the knee there exists a pure sprain without a bony or a ligamentous lesion, which is merely the vasomotor translation of sudden excitation of the sensitive ligamentous endings. Local infiltration of procaine hydrochloride will cure this type of sprain within forty-eight hours. The author concludes, from surgical exploration of

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31. Leriche, R.: De l'entorse et de la luxation du genou; question de définition et de thérapeutique d'après trente-neuf opérations, J. de chir. 54:593-603 (Dec.) 1939.

a good many knees, that true rupture of the internal lateral ligament is rare. The ordinary type of severe sprain usually results in partial avulsion of the tibial spine or rupture of the crucial ligaments.

The injected procaine hydrochloride does not act purely as a local anesthetic for the ligaments but acts on the vasomotor system. The procaine hydrochloride should be free of epinephrine.

ED. NOTE: It is difficult to evaluate the severity of the lesions about which Leriche writes, and, accordingly, this treatment should be applied with the utmost caution. One may assume that the bony fragment is from the external malleolus or a chip from the scaphoid bone. It is rarely necessary to remove either of these fragments if they are small. One may treat by strapping similar to that used in the treatment of sprains.

#### OSSEOUS CHANGES IN CERTAIN DISEASES

*Hodgkin's Disease.*—Goldman<sup>32</sup> analyzes 212 cases of Hodgkin's disease. The disease shows a preponderance among men between 20 and 40 years of age. There are no demonstrable predisposing factors in any case. In 79 per cent of the series enlargement of the lymph nodes was the first abnormality drawing attention of the patient to his condition. Unilateral lymphadenopathy was more common than symmetric involvement in the early stages. Discharging sinuses occurred in 7 cases, possibly indicative of concomitant tuberculosis. Splenomegaly was infrequent in the early stages, but its incidence was almost 100 per cent in postmortem studies. In no instance was there enlargement of mediastinal nodes without palpable cervical, supraclavicular or axillary adenopathy. Roentgen examination of the mediastinum revealed nothing characteristic. In 19 cases the parenchyma of the lung was involved. The skin was involved in 38 per cent (80 cases). The osseous system, in which the orthopedist is mostly interested, showed roentgen changes in only 6.6 per cent of the cases. Roentgenograms of the skeleton were taken only when pain or deformity warranted it. The most frequent areas of involvement were, in the order named, the vertebral column, the pelvis, the ribs, the upper ends of the femurs and the sternum. Less frequently the ends of the humeri and other long bones and the skull were involved. There was no characteristic roentgen picture of these foci. They were most frequently osteolytic, closely resembling metastatic carcinoma. Less frequently osteoblastic changes were found. The osseous lesions of Hodgkin's disease are less painful and more radiosensitive than metastatic carcinoma. Two cases of Hodgkin's disease have been reported in which there were lesions of bone marrow without apparent involvement of the lymph nodes.

32. Goldman, L. B.: Hodgkin's Disease: Analysis of Two Hundred and Twelve Cases, J. A. M. A. **114**:1611-1616 (April 27) 1940.

ED. NOTE: Geschickter and Copeland found that the bone marrow is more frequently involved in Hodgkin's disease than is usually suspected. According to autopsy reports, the bones may be involved in 40 per cent of the cases. Roentgenograms taken periodically revealed that it was only after a considerable time had elapsed that changes in the density of the bone were noted. The lesion may appear osteoplastic or osteolytic, and in the long bones it usually makes its appearance near the proximal end. Later the entire long bone may be involved. Apparently the vertebral bodies are the bones most frequently affected.

#### NEOPLASMS

*Xanthoma of Tendon Sheaths and Synovial Membranes.*—Galloway and his associates<sup>33</sup> report 70 cases of xanthoma of the tendon sheaths treated at the Mayo Clinic. In addition, they have made a comprehensive review of the literature, in which were reported the cases of 317 patients with 327 tumors. The cases are divided according to the patients' age, size of the tumor, sex, duration, etc.

The authors are convinced that the primary factor in the production of this tumor is a preexisting alteration in lipid metabolism in which there is either a marked disturbance in the absolute values for blood lipoids or, even more important, a disturbance in the ratio of the various constituents, chiefly that of cholesterol to cholesterol esters. Given this setup plus the secondary factor, which is trauma or an infection at the site of the lesion, a xanthoma results. When the secondary factor enters the picture, minute hemorrhages occur within the tissue. Lipoids and pigment are deposited by way of the circulation, and then a secondary response of the tissue occurs in which certain endothelium-like cells, foam cells, foreign body giant cells and adult connective tissue make their appearance. The rapidity of growth varies with the amount of hemorrhage and the subsequent release of pigment. As the condition progresses, vascularity increases; more hemorrhage occurs, and a "vicious circle" is established. Likewise, repeated traumas will increase the rate of growth.

The authors state the belief that the tumor is benign and have failed to find any evidence of metastases.

Given a patient about 40 years of age with a painless, slow growing, firm, rounded, subcutaneous mass located on or associated with a tendon, usually a flexor of the finger, plus a history of previous trauma and an altered lipid metabolism, a diagnosis of xanthoma is likely. In the knee the symptoms are those of a derangement. In cases in which

33. Galloway, J. D. B.; Broders, A. C., and Ghormley, R. K.: Xanthoma of Tendon Sheaths and Synovial Membranes: Clinical and Pathologic Study, Arch. Surg. 40:485-538 (March) 1940.

aspiration can be done, a high cholesterol content of the aspirated fluid is positive evidence of the presence of a xanthoma.

Differential diagnosis is made by biopsy. The treatment is complete surgical removal.

ED. NOTE: These are the tumors most often associated with the synovial membrane. It has been established that no coincidence of articular xanthoma with systemic forms of xanthomatosis exists.

#### SPINE

*Pathology of the Intervertebral Disk.*—Saunders and Inman<sup>34</sup> have given a complete review of the anatomy, physiology and pathology of the intervertebral disk. They state that in cases of juvenile kyphosis the degeneration of the disk commences early and is well established by the second decade. In "chip fractures" of the vertebral body there is trauma to the cartilage plate, and such fractures are often followed by collapse and thinning of the disk.

They state the belief that the osteophytes which form with certain types of arthritis of the spine occur "in the superadded tissue which is developed as a repair mechanism in response to the increasing strain thrown on the peripheral junction by the progressive collapse of the disk and the development of shearing forces set up in the lateral displacements of the vertebral segments as in the scoliosis of arthritis deformans."

It is said that posterior displacements of the disk tissue are formed with greatest frequency in the spinal columns of elderly persons. The authors express the belief that the nodules seen in the spinal canal at operation may be either herniations of the nuclei pulposi or protrusions of intervertebral disks. They state that in a great majority of instances posterior herniations are evidences of general disk degeneration.

In adolescent kyphosis "in the vast majority of cases sizable herniations of the nuclear material into the spongiosa are indicated by sclerosis of the adjacent bones." In senile kyphosis the essential pathologic process is pressure necrosis of the anterior portion of the intervertebral disk.

In spondylosis deformans there is a generalized disk degeneration. There is a dissolution with loss of substance in the nucleus pulposus, followed by relaxation and protrusion of the annulus about the periphery, which leads to a lateral shifting of the vertebral bodies with the strain on the ligamentous structures. There is formation of osteophytes. These osteophytes appear earliest in those areas of the spinal column which are subjected to the greatest amount of motion.

34. Saunders, J. B. deC. M., and Inman, V. T.: Pathology of Intervertebral Disk, Arch. Surg. 40:389-416 (March) 1940.

## HAND

*Luxation of Extensor Tendons in the Hand.*—Straus<sup>35</sup> contributes 1 case of luxation of an extensor tendon of the hand and discusses 13 cases collected from the literature. He classifies them after Maydl as due to pathologic softening of the structures in the vicinity of the metacarpophalangeal joint and to trauma. The traumatic group may be further divided into those in which the dislocation is caused by a direct blow on the metacarpophalangeal joint and those due to indirect violence caused by contracture of the extensor tendon against resistance or by external force causing flexion of the finger against muscular resistance. It seems that the dislocation always occurs at the metacarpophalangeal joint, and the displacement was toward the ulnar side in all but 1 of the cases studied. The middle finger was involved in 10 cases and the index finger in 3.

The patients give a history of trauma, which may be trivial or severe, and the trauma is followed by disability and swelling on the dorsum of the hand. The swelling and the acute pain disappear within a few days, but impairment of extension persists. In cases of longer involvement, with the fingers in extension the hand may appear normal, but as flexion of the proximal phalanx approaches 45 degrees a jerk in the movement is observed and the finger jumps into a position of ulnar deviation. Flexion can then be completed with the finger in ulnar deviation. With extension the movement is locked or impeded at 45 degrees, and frequently assistance is required to straighten the finger beyond this point. Again there is a visible jump as the extensor tendon slips back onto the head of the metacarpal bone. A similar disability is seen in cases of "trigger finger" or "spring finger."

A good functional and anatomic result is obtained by operative repair, in which a retention sling is fashioned from the fibrous tissue just proximal to the metacarpal head and associated lacerations of tendon and capsule are sutured.

## FOOT

*Cavus Feet.*—Thirty-three of 200 patients operated on who responded to a request for examination form the basis for the report of Brewster and Larson.<sup>36</sup> Poliomyelitis was the etiologic factor in 24 of these cases, spina bifida in 3, idiopathies in 3, Friedreich's ataxia in 1, clubfoot in 1 and arachnodactylia in 10. Twenty patients were females, and 13, males. The cases were divided into three groups, according to the type of operation performed. In group 1 this was plantar fasciotomy, etc.; in

35. Straus, F. H.: *Luxation of Extensor Tendons in Hand*, Ann. Surg. **111**:135-140 (Jan.) 1940.

36. Brewster, A. H., and Larson, C. B.: *Cavus Feet*, J. Bone & Joint Surg. **22**:361-368 (April) 1940.

group 2, triple arthrodesis, and in group 3, triple arthrodesis plus transplantation of the extensor tendons to the metatarsal necks. The best results were obtained in the 9 cases in which the group 3 procedure was carried out.

A modified type of triple arthrodesis is described. The astragalus is reshaped in order to elevate the forefoot and flatten the long arch; the os calcis is set back to increase leverage of the achilles tendon, and the foot is shortened to relax the tightness of the plantar fascia and lessen the "cock-up" position of the toes.

ED. NOTE: Cole emphasizes that true clawfoot is a symptom and not an entity. He feels that a so-called anterior tarsal wedge osteotomy which does not destroy the talonavicular or the calcaneocuboid joints gives satisfactory results. He states that if a wedge of bone which destroys the midtarsal joint is to be removed a complete triple arthrodesis should be performed at the same time. When he transplants the extensor tendons, he inserts them proximally into the cuneiform bones rather than into the metatarsal heads or necks.

*Metatarsalgia*.—Betts<sup>37</sup> discusses the history, etiology, symptoms and treatment of metatarsalgia. Of 10 patients operated on by himself and 9 operated on by his colleagues, each had a neuroma. In each case the fourth digital plantar nerve was involved. The author states the belief that the neuroma is the result of the anatomic formation and location of the nerve. It is formed by the internal plantar nerve and a communicating branch from the external plantar nerve, each coming from opposite sides of the belly of the flexor brevis muscle and crossing it obliquely before uniting. Two or three centimeters distal to this it divides to pass to adjacent sides of the third and fourth toes. As a result it is thicker than other digital nerves, and the thicker part lies on the transverse ligament. The flexor brevis muscle contracts, fixing its origin, and the dorsiflexion of the toes in walking stretches the nerve around the unyielding transverse ligament.

The pain, numbness and tingling which follow attacks are frequently diffuse. There is dulness of sensation on adjacent sides of the third and fourth toes. Deep pressure over the neuroma produces no acute pain, and only slight tenderness is present. Manipulation of the foot and toes gives negative results. Vascular and trophic changes are occasionally present. The foot is not flat or weak but is usually fairly well shaped, with frequently a slight clawing.

Satisfactory results were obtained from a plantar neurectomy through a longitudinal incision between the fourth and the third metatarsal head.

37. Betts, L. O.: Morton's Metatarsalgia: Neuritis of the Fourth Digital Nerve. *M. J. Australia* 1:514-515 (April 13) 1940.

## ORTHOPEDIC OPERATIONS

*Osteoclasia for Supination Deformities.*—Blount<sup>38</sup> discusses the supination deformities of the forearm which not infrequently follow poliomyelitis or flaccid paralysis (the forearm type of brachial palsy) at birth. The persistent supination renders ineffective an otherwise useful hand and is cosmetically objectionable.

Roentgenograms of the forearm of a patient with this deformity showed bowing of the bones and a degree of osteoporosis usually seen after prolonged fixation in plaster of paris. This rarefaction suggested to the writer the possible value of osteoclasia in correcting the deformity. The author reports the end results in 9 cases in which fracture of both bones of the forearm in the middle third was easily accomplished over a padded wedge. In 1 case it was necessary to use the Thomas wrench in addition to the padded wedge.

In these 9 cases, 5 good results and 4 fair or poor results were obtained. It is noteworthy that it was in the earlier cases that the least satisfactory results were obtained. It was found that there is usually a rapid loss of part of the correction and that gradual partial recurrence of the deformity takes place. Accordingly, all possible pronation up to 90 degrees should be maintained in plaster for four to six weeks. Frequently an increase rather than a diminution of the range of motion is obtained, and this motion is through a more useful arc.

*Shelf Operation for Congenital Dislocation of the Hip.*—West<sup>39</sup> prefers to term the shelf operation "acetabulum reconstruction" and discusses his method of treating congenital dislocation of the hip at the different age periods, apart from the "ideal abduction treatment during the first twelve months of life."

He feels that the type of treatment to be followed is more or less dependent on the age of the patient at the time of starting treatment. Accordingly, he divides the patients into four age groups. For the first, between 1 and 3 years of age, he performs a closed reduction and follows this with the usual immobilization in plaster of paris for about nine months. At the end of this period roentgenograms are made to determine whether the upper lip of the acetabulum is developing. If it is developing nothing more need be done, but if there is no sign of a lip he immediately performs a "shelf operation."

Treatment of patients between 3 and 5 years of age requires considerable judgment on the part of the surgeon. When he finds that there is no sign of the development of an upper acetabular lip but, instead, a

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38. Blount, W. P.: Osteoclasia for Supination Deformities in Children, *J. Bone & Joint Surg.* **32**:300-314 (April) 1940.

39. West, E. F.: Shelf Operation for Congenital Dislocation of Hip, *M. J. Australia* **1**:513-514 (April 13) 1940.

groove in this location, he proceeds with his reconstruction operation. For unilateral dislocations, when the acetabulum shows "fair" development and there are signs of the formation of an upper lip he first tries a closed reduction. Then, after the patient has remained in plaster for six months with the femoral head in position, if the upper lip shows signs of developing the result will be satisfactory. For bilateral dislocations he usually operates immediately because of the tendency for one hip to remain in place and the other to redislocate because of acetabular inadequacy.

He states the opinion that attempts at closed reduction of the hip in children between 5 and 8 years of age may result in damage to the upper femoral epiphysis or in the later development of absorptive arthritis from excessive pressure of the head against the acetabulum. Accordingly, he feels that it is better to pull the head down so that it is opposite the acetabulum, either by weight extension or by Anderson's well leg traction, and then to perform a reconstructive operation.

He has found that a closed reduction is usually impossible after the patient has reached his eighth year, and in cases in which the femoral head is in an anterior position no treatment is required, because function is satisfactory. Treatment with the head in the posterior position at this and later stages is not discussed except as regards the question of formation of a shelf at the site of the deformity. He is not in favor of the latter procedure, because he feels that it does nothing to correct the length of the extremity or the lordosis, and the results do not appear to make the operation worth while.

He prefers the term "acetabular reconstruction" because he feels that one should aim at turning down the upper, flattened-out portion of the acetabulum, which is covered by cartilage, and at reconstruction of the normal hemispheric shape of the acetabulum. The portion turned down is fixed with a graft from the iliac crest and fastened with two bone pegs. He uses traction to the extremity before and during the operation. He avoids opening the capsule unless it is necessary to clear away fibrous or fatty tissue. Postoperative care is first on a Jones abduction frame, with the traction maintained. After ten days the child is placed in well leg traction. The traction is removed after six to eight weeks, and a hip spica is applied for an additional six weeks. Then (after three months) the child is permitted to move the extremity in bed for four weeks before attempting to walk.

ED. NOTE: The author's statement regarding cases in which the femoral head is in an anterior position may arouse considerable controversy. McCarroll and Crego maintain that there are primary anterior congenital dislocations of the hip and have reported their experiences



with 10 cases. They feel that this type is responsible for some of the unsatisfactory results obtained in treating congenital dislocation of the hip.

*Femoral Osteotomy for Diseases of the Hip Joint.*—King<sup>40</sup> feels that the mechanical or weight-shifting osteotomies of Lorenz and the later modifications by Schanz are among the most gratifying operations in orthopedic surgery because they can be relied on to insure a stable and painless hip. Their disadvantages are three to four months' immobilization, with the associated weakening of the patient, and the fact that they are dangerous procedures to perform on elderly persons. He avoids stiffness of the hip, however, by traction on and abduction of the extremity.

He discusses his technic and results in 52 cases of disease of the hip treated in this manner. Twenty-six of the patients were operated on for intractable pain caused by osteoarthritis of the hip. In none of this group did the operation fail to relieve pain. He does not recommend this operation for recent fractures of the femoral neck, but he obtained satisfactory results with 12 young and middle-aged adults for whom the Smith-Petersen nail had failed or union had occurred with crippling osteoarthritic degeneration of the joint. For such patients osteotomy is useless if there is a fixed deformity, such as compensatory spinal curvatures or a stiff knee. In many "late cases" of "slipped epiphysis" (adolescent coxa vara), he feels that there is a definite advantage in performing an osteotomy rather than the dangerous intra-articular operation, because the late functional results are excellent and the anatomic reconstruction is surprisingly good. The operative technic which he used for 7 of these patients is given in detail. The Lorenz osteotomy can reasonably be performed after a "blind arthrodesis" (tibial graft through the trochanter into the ilium away from the diseased area) on adults who, despite improvement following conservative treatment, still have a long-standing, uncured disease and on children after two or three years of treatment if the disease is not cured and is causing an adduction deformity. Finally, he has done this operation in 2 cases of dislocated hips. In 1 of these the dislocation followed old septic arthritis, and in the other it resulted from trauma and had redislocated. In the second case it was complicated by osteoarthritis. Good results were obtained in both cases.

ED. NOTE: During the last ten years McMurray has performed oblique osteotomy on 42 patients with osteoarthritis of the hip joint. After division of the femur, he places the sharp end of the shaft inward directly under the cotyloid ligament of the acetabulum. This transfers

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40. King, T.: The Value of Femoral Osteotomy for Diseases and Injuries of the Hip Joint, M. J. Australia 1:253-268 (Feb. 24) 1940.

some of the body weight directly through the pelvis to the shaft of the femur. In addition, it rotates the head of the femur so that a new portion of the articular surface takes the remaining weight. This results in a painless hip and a retention of 50 per cent of motion. McMurray finds that the procedure may be performed in ten to fifteen minutes and that this is of importance in the case of elderly patients.

#### RESEARCH

*Autogenous Rib Cartilage Grafts to Repair Surface Defects in Dog Joints.*—Young<sup>41</sup> cites the work of Shands, Key, Bennett and Bauer to show that experimental wounds in cartilage heal but do so imperfectly. Young undertook experiments to determine whether autogenous costal cartilage grafts would promote better healing in traumatic articular cartilage defects. He used dogs in his experiments, grafting costal cartilage to defects in the superior patellar groove between the nonweight-bearing superior extensions of the patellar condyles. The defects were made down to subchondral bone. He gathers from his experiments that "rib cartilage grafts placed in parallel on the denuded joint surface healed together by cartilaginous union; whereas articular cartilage and rib cartilage always united by fibrous tissue. Gross and microscopic studies show that these grafts healed in place by fibrous tissue connections and remained viable for as long as a year. At eighteen months there was partial replacement of the graft by osteoid tissue which could probably be explained on a technical basis."

*Bone Marrow in Bone Regeneration.*—Levander<sup>42</sup> experimented with adult and young rabbits to determine the bone-regenerating activity of bone marrow. In adult rabbits the bone marrow from the marrow cavity of the radius and ulna was placed subcutaneously. In 5 of 12 animals bone formation was observed in periods varying from fourteen to fifty-eight days. There was no formation of cartilage. In 9 young rabbits similar experiments were performed. Microscopic examination was made of the grafted area two to eleven days after transplantation of the marrow. The author found that the transplanted marrow died in each case. Bone formation arose from the mesenchymal tissue formed around the graft. Bone formation was observed early (within six days). It was concluded that the marrow stimulated bone formation through some inherent substance which influenced the nonspecific mesenchymal tissue. A review of the literature on bone formation is given.

41. Young, F.: Use of Autogenous Rib Cartilage Grafts to Repair Surface Defects in Dog Joints, *Surgery* 7:254-263 (Feb.) 1940.

42. Levander, G.: Experimental Study of Role of Bone Marrow in New Bone Regeneration, *Acta chir. Scandinav.* 83:545-560, 1940.

ED. NOTE: It would be interesting to know the author's technic for removal of the bone marrow and whether traces of endosteum were taken with the material for implantation.

*Calcium and Phosphorus Metabolism in Osteomalacia.*—Liu and his associates,<sup>43</sup> because it has been suspected that infants of osteomalacic mothers might show disturbed calcium and phosphorus metabolism, have observed 4 nursing mothers, studying the calcium, phosphorus and nitrogen metabolism of the mother and the child simultaneously. During their investigation all material excreted was carefully analyzed and correlated with the intake. Their observations are divided into four groups. In the first group of cases the mother had healing osteomalacia with good retention of calcium and an abundant store of vitamin D during gestation, and the infant was born normal. During lactation the mother maintained herself in mineral balance on a relatively high intake, while the infant retained the major portion of the calcium-phosphorus intake in milk.

The second set consisted of a mother with osteomalacia and tetany and an infant with rickets and tetany. Both showed poor retention of calcium and phosphorus, but after vitamin D therapy of the mother both showed improvement. As a result, the mother was able to absorb sufficient minerals not only for the requirements of lactation but to improve her skeletal store. The infant showed markedly improved mineral retention.

The third experiment was on a normal wetnurse supplying breast milk to a rachitic child born of an osteomalacic mother. To maintain balance the wetnurse had to have her calcium intake raised to 1.5 to 2 Gm. Part of the ability to balance is attributable to administration of vitamin D. The infant had been fed a klin formula and breast milk prior to administration of vitamin D to the wetnurse and showed poor calcium and phosphorus metabolism. After administration of vitamin D the infant was much improved in mineral retention as well as in rachitic osseous changes.

In the final series the mother had had sufficient vitamin D to give birth to a normal infant. During lactation, while vitamin D was being withheld, she began to show a negative mineral balance on a high intake. Later, with the administration of vitamin D there was good retention of calcium and phosphorus. The infant showed good mineral retention throughout the period of study, but as the mother was being depleted of vitamin D the urinary calcium diminished and then disappeared,

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43. Liu, S. H.; Chu, H. J.; Su, C. C.; Yu, T. F., and Cheng, T. Y.: Calcium and Phosphorus Metabolism in Osteomalacia, *J. Clin. Investigation* 19:327-347 (March) 1940.

corresponding to an increase in the stool. This is interpreted as an early sign of vitamin D deficiency, for subsequent administration of vitamin D induced a reversal in calcium secretion in favor of the urine.

#### PHYSIOLOGY

*Physiology of Articular Structures.*—Bauer, Ropes and Waine<sup>44</sup> have carefully reviewed and discussed the literature concerning the anatomy and physiology of articular structure. An excellent bibliography is presented with the paper. In the discussion of joints as structural and functional units, the authors attempt a synthesis of the evidence by integrating the individual results into a working scheme. All principal joint components have a common mesenchymal origin. The viscous synovia aids by its cohesive action in uniting the articular ends and forms a fluid on which the cartilaginous surfaces glide with negligible friction. The disappearance of vascular and neural elements from cartilage at the time of birth may be explained by the unusual strain which is imposed on this tissue. Its subsistence depends for the most part on the synovial fluid. Since arterial blood does not come in contact with cartilaginous cells, the breakdown of glycogen must take place through anaerobic oxidation. This is confirmed by the low respiratory quotient of this tissue. The notable predominance of matrix over cells reflects both the physical requirements made on cartilage and the metabolic conditions under which it functions.

The distribution of electrolytes and nonelectrolytes between the blood and the synovia and the marked vascularity of the synovial membrane indicate that the fluid is a dialysate of blood plasma. It contains an admixture of albumin, globulin and mucin. The slight capillary permeability is probably responsible for the presence of the albumin and the globulin, and it has been suggested that mucin is formed by the connective tissue cells of the synovialis and carried into the joint by the plasma dialysate as it diffuses through the synovial tissues. The opposing forces of capillary pressure and osmotic pressure difference between plasma and fluid determine the volume of fluid present. Substances entering the joint from the systemic circulation must pass the capillary endothelium and diffuse through the interstitium of the synovialis. The concept of synovial tissues as a membrane analogous to the true body membranes should be discarded, because uninterrupted continuity exists between the intercellular fluid of the synovialis and the synovia. Synovial tissue has much greater permeability than true membrane. Small molecules are resorbed almost entirely by the blood vascular system, while the larger protein molecules are removed with difficulty and only by way

44. Bauer, W.; Ropes, M. W., and Waine, H.: *Physiology of Articular Structures*, *Physiol. Rev.* 20:272-312 (April) 1940.

of lymphatics. Mononuclear phagocytes are the predominant cellular constituent of the synovial fluid, and they carry the particulate matter and cellular debris into the lymphatics. A balance of the aforementioned factors is necessary for maintenance of a normal amount and composition of synovial fluid in the joint cavity. The slightly negative intra-articular pressure, varying with motion, also appears to be part of this equilibrium.

Deviations from normal articular physiology consist chiefly of alterations in the synovial tissue and changes in the intra-articular metabolism. The former leads to disturbances of the exchange equilibrium, while the latter results mainly in deficient supply of nutriment to cartilage. Injured cartilage shows little or no tendency to regenerate, and repairs take place by invading fibrous tissue.

There is evidence that synovial fluid is an example of tissue fluid in general, and it is indicated that the articular lumen represents a connective tissue space.

ED. NOTE: The controversy regarding the production of plasma dialysates in general has not been closed, and the presence of mucin within the synovia would seem to segregate the latter from tissue fluids as they are usually understood.

## SIGNIFICANCE OF MAMMARY DISCHARGE IN CASES OF PAPILLOMA OF THE BREAST

### A CLINICAL AND PATHOLOGIC STUDY

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It is our purpose to present the results of a clinical and pathologic study of 227 cases of papilloma of the breast and to emphasize particularly the fact that discharge from the nipple, of any nature whatsoever, was found to be of great significance. We are aware that this view is not in accord with that of at least one great authority on the subject.<sup>1</sup> Views change as evidence accumulates, however, and we believe that benefit will accrue from publication of our data. Our material is presented mainly in the accompanying table. The percentages in this table are carried out to one decimal place; when it is necessary to repeat them in the text they are given only in whole numbers.

### BENIGN PAPILLOMA

The average age of the 109 patients with benign papilloma was 46 years; the youngest was 19 and the oldest 78 years of age. All but 1 of the patients were women; 80 per cent of the women had been married. A family history of carcinoma was related by 19 per cent of the patients. Medical advice had been obtained by 29 per cent before they were seen at the clinic. Previous surgical treatment of the breast had been given to 5 per cent, two thirds of whom had undergone local excision of a lesion the exact nature of which was not known. The remaining third of this 5 per cent of patients, because of carcinoma graded 3 or 4, had submitted to previous radical amputation of the breast other than the one under consideration in this study. The patients had recognized that an abnormal condition of the breast existed for an average of a year

From the Division of Surgery, the Mayo Clinic.

1. Bloodgood, J. C.: The Changing Clinical Picture of Lesions of the Breast, *Am. J. M. Sc.* 179:27-47 (Jan.) 1930; Benign Lesions of Female Breast for Which Operation Is Not Indicated, *J. A. M. A.* 78:859-863 (March 25) 1922.

and a half before they visited the clinic. The chief complaint of 87 per cent on admission concerned the breast. The complaint of 81 per cent was specifically of discharge from the nipple; this discharge was

*Papilloma of the Breast*

	Malignant		Benign	
	Number	Per Cent	Number	Per Cent
Cases.....	118	51.9	109	48.0
Civil state, women:				
Married.....	104	88.1	86	79.8
Single.....	13	11.0	22	20.1
Males.....	1	0.84	1	0.9
Family history of cancer:				
Positive.....	28	23.7	21	19.2
Negative.....	90	76.2	88	80.7
One or more pregnancies.....	71	60.1	60	55.0
Previous operation on breast:				
Local excision of lesion (same breast)*.....	10	8.47	4	3.6
Simple mastectomy (other breast)*.....	3	2.5	..	....
Radical mastectomy (other breast)*.....	4	3.3	2	1.8
Total.....	17	14.2	6	5.42
Chief complaint:				
Concerned breast.....	107	90.7	95	87.0
Did not concern breast.....	11	9.0	14	12.8
Positive history of trauma.....	7	5.9	8	7.3
Patients with discharge.....	87	73.8	88	80.7
Patients without discharge.....	31	26.2	21	19.2
Discharge from nipple:				
Serous.....	34	28.8	34	31.1
Serohemorrhagic.....	25	21.1	28	25.6
Hemorrhagic.....	28	23.7	26	23.8
Palpable tumor on examination.....	61	51.7	30	27.5
No palpable tumor.....	57	48.3	79	72.4
Discharge present with no palpable tumor.....	52	44.0	..	....
Previously in physician's care.....	45	38.9	32	29.3
Surgical procedure:				
Local excision of lesion.....	1	0.84	7	6.4
Simple mastectomy.....	54	45.7	91	83.4
Radical mastectomy.....	63	53.3	1	0.9
Bilateral simple mastectomy.....	..	....	10	9.1
Breast involved:				
Left.....	79	66.9	51	46.7
Right.....	37	31.3	54	49.5
Both.....	2	1.6	4	3.6
Grade of malignant papilloma (Broders):				
Grade 1 carcinoma.....	81	68.6	..	....
Grade 2 carcinoma.....	33	27.9	..	....
Grade 3 carcinoma.....	2	1.7	..	....
Grade 4 carcinoma.....	2	1.7	..	....
Lymph nodes involved.....	3	2.5	..	....
Postoperative roentgen therapy.....	54	45.7	..	....
Subsequent operation on breast:				
Local excision of lesion (same breast)*.....	1	0.84	..	....
Simple mastectomy (other breast)*.....	8	6.7	..	....
Radical mastectomy (other breast)*.....	7	5.9	..	....
Total.....	16	13.5	11	10.0

\* By "same breast" is meant the breast concerned in the study reported here; by "other breast" is meant the breast other than the one concerned in the study reported here.

serous, hemorrhagic or serohemorrhagic in about an equal number of instances. As can be seen in the table, the character of the discharge, as compared with that observed in the group in which malignant lesions were found, was not an indication of the malignancy or benignancy of the lesion. Discharge from the nipple had been present on the average

for a year and four months. In only 28 per cent of cases was a tumor palpable. Simple mastectomy was done in 83 per cent of cases; local excision in 6 per cent, and radical mastectomy in 1 case. The patient in this solitary case was one of those who had previously undergone a similar procedure on the other breast. Any other procedure employed is listed in the table.

#### MALIGNANT PAPILLOMA

The average age of the 118 patients with malignant papilloma was 47 years; the youngest was 19 and the oldest 87 years of age. All but

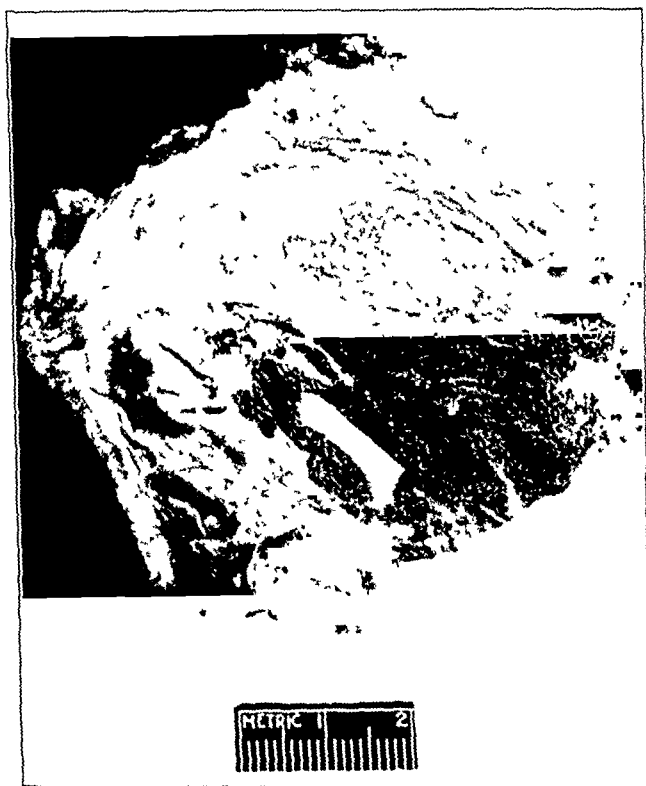


Fig. 1.—Cross section of the nipple and the adjacent tissue of the breast. The nipple is at the left; the arrow points to several dilated ducts filled with the papillary tumor.

1 of the patients were women. Eighty-eight per cent had been married. The man in this group had had a serous discharge from the nipple for seven months, which was not associated with a palpable tumor. On examination he was found to have a carcinomatous papilloma of grade 3. A family history of carcinoma was related by 24 per cent of the patients, slightly more than in the preceding group. Medical advice had been obtained by 39 per cent before they came to the clinic. Fourteen per cent had submitted to previous surgical treatment of the breast, some-



what more than half of whom had undergone local excision of a lesion the exact nature of which was not known. Slightly more than a sixth of this 14 per cent had submitted to simple mastectomy and slightly less than a fourth to radical mastectomy. The patients had recognized that an abnormal condition of the breast existed for an average of two and a fourth years before they were examined at the clinic. The chief complaint of 91 per cent on admission concerned the breast, whereas the chief complaint of 9.3 per cent was referable to some other organ.



Fig. 2.—Papillary adenocarcinoma, grade 1 ( $\times 90$ ).

Seventy-four per cent of patients complained of discharge from the nipple, and, as was noted of those with benign tumor, the discharge was serous, hemorrhagic or serohemorrhagic in an almost equal number of instances. Discharge from the nipple had been present for an average of a year and three fourths. Slightly more than half of the patients had palpable tumors, and slightly less than half (52, or 44 per cent) had noted a discharge in the absence of a palpable tumor. Of these 52 patients, the tumors of 44 were classified by the pathologist as papillary adenocarcinoma grade 1 (figs. 1 and 2), those of 7 as grade 2 and that

of 1 as grade 3. Simple mastectomy was performed on 46 per cent of the 118 patients and radical mastectomy on 53 per cent. One patient was subjected to local excision only, but radical mastectomy was done later. The lesion occurred more than twice as frequently in the left as in the right breast. Carcinoma of grade 1 and of grade 2 was found, respectively, in 69 and 28 per cent of cases, and papillary adenocarcinoma of grade 3 and of grade 4 each was found in 2 per cent. The lymph nodes of only 3 per cent of patients were involved.

Forty-six per cent of patients with malignant papillomas received postoperative roentgen therapy. Fourteen per cent returned for further surgical treatment of the breast. Half of these underwent simple amputation, and slightly less than half underwent radical amputation of the breast other than the one which had been the site of neoplasm at the time of the patient's previous visit to the clinic; 1 patient was subjected to local excision of cutaneous nodules and axillary lymph nodes. There were no deaths in the hospital, but 3 patients died as a result of recurrence or metastasis of the malignant lesion. All of these had undergone radical mastectomy primarily. One patient, who had carcinoma of grade 1, died three years after operation; 1 died a year after operation on the second breast for carcinoma of grade 3, and 1 died nine years after the first operation, from carcinoma of grade 4, which affected the breast other than the first one involved.

#### COMMENT

Much confusion and difference of opinion have resulted from the vast number of papers written on the subject of discharge from the nipples. Many physicians still maintain the belief that discharge from the nipple in the absence of a demonstrable tumor may be of slight concern or can be disregarded. From a study of the clinical records, we have been impressed by the fact that many patients with discharge from the breast have been advised to do nothing about it, to use local applications, to "watch the discharge" or to report for periodic examinations; only infrequently has surgical treatment been advised. There seems to be general agreement among physicians that discharge from the nipple when a tumor is present is significant; in most instances biopsy of the lesion is advised. We wish to emphasize that in 48 per cent of our series of patients with malignant papillomas no tumor was demonstrable. No tumors were palpable in 60 per cent of all patients with malignant papillomas who had experienced discharge from the nipple.

In view of the evident difference of opinion that exists regarding the significance of papillomas of a low grade of malignancy that occur in the breast, this communication was submitted to Dr. W. C. MacCarty and to Dr. A. C. Broders for comment. Dr. MacCarty referred us to

an article by him<sup>2</sup> in which he discussed pathologic considerations of lesions of the mammary gland and in a personal communication made the following comment:

I have never seen a breast with serous or bloody discharge in which, at operation, I did not find a papilloma, frequently more than one. These are not necessarily palpable. Some of the papillomata are definitely histologically and cytologically malignant. The great clinical difficulty is to find out which breast with a discharge contains a benign papilloma and which a malignant papilloma. The differential diagnosis must be made with a microscope. In my opinion, a breast with continued serous or bloody discharge should be removed as a simple mastectomy. If the lesion is found to be histologically and cytologically malignant, a complete operation should be performed. I believe your conclusions in the paper are conservative and justifiable.

Dr. Broders responded as follows: "Dr. McDonald and I have gone over this paper very carefully. We are of the opinion that your conclusions are fundamentally sound."

In the light of such evidence, therefore, we feel that it is imperative that discharge from the nipple, regardless of its character and regardless of whether a tumor is demonstrable, be given serious consideration and that in most instances surgical treatment be advised, in order that the exact nature of the lesion may be determined.

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2. MacCarty, W. C.: *The Mammary Gland: Pathological Considerations*, in Piersol, G. M., and Bortz, E. L.: *The Cyclopedia of Medicine, Surgery and Specialties*, Philadelphia, F. A. Davis Company, 1939, pp. 523-543.

# CARCINOMA OF THE LUNG

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AND

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NEW ORLEANS

Until relatively recently the diagnosis of cancer of the lung inevitably signified a rapidly tragic outcome. Within the past six years, however, many patients with pulmonary malignant tumor have been spared this death sentence by the successful removal of the cancerous lung. Of even greater importance is the increasing incidence of such survivals. The successes in the earlier cases were few because of late diagnoses and also because preoperative preparation, anesthesia and operative technic were inadequately developed. Recently, because of early diagnoses as well as improvement in surgical management, the prognosis of pulmonary carcinoma has become relatively favorable.

## INCIDENCE

Until relatively recently carcinoma of the lung was considered infrequent. Adler collected 374 cases of carcinoma of the lung in 1912 and stated: "On one point, however, there is nearly complete consensus of opinion and that is that primary malignant neoplasms of the lung are among the rarest forms of disease." Whereas this opinion may have been justified in 1912, statistical facts indicate an antithetic point of view today. Carcinoma of the lung at present is second in incidence to carcinoma of the stomach, as is evidenced by the reports of Brines and Kenning and Koletsky. In both of these reports the conclusions were based on autopsy series and are, therefore, absolute and not relative. Brines and Kenning found that among 936 patients admitted to the tumor clinic carcinoma of the lung was fourth, being preceded by carcinoma of the stomach, of the uterine cervix and of the breast. These, however, were clinical series and were less accurate than the autopsy series. Koletsky observed that the lung ranked second only to the stomach as the primary site of carcinoma in 7,685 consecutive cases studied post mortem. Kikuth similarly found that of the sites affected by carcinoma the lung was second.

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Presented at the International Cancer Congress, Atlantic City, Sept. 13, 1939.

Although there is considerable controversy concerning the increased incidence of carcinoma of the lung, many believing that the increase is apparent and not real, there can be no question from the reported autopsy statistics that the incidence of carcinoma of the lung is absolutely increasing. Weller found that of the first 1,000 autopsies at the University of Michigan Hospital carcinoma of the lung occurred in 0.1 per cent. In the second thousand autopsies the incident was 0.5 per cent, and for 450 cases in the third thousand the incidence was 0.8 per cent. Assmann found that in the department of pathology of the University of Leipzig the incidence of carcinoma of the lung in all autopsies from 1900 to 1906 was 0.67 per cent and that 5.01 per cent of all carcinomas were pulmonary. From 1919 to 1922 the pulmonary malignant tumor was observed in 1.54 per cent of all autopsies and the incidence of carcinoma of the lung was 9.17 per cent of all carcinomas. Holzer obtained similar figures, which, however, are even more significant. From 1895 to 1904 the percentage of carcinoma of the lung in all autopsies was 0.7, and the incidence of carcinoma of the lung was 1.04 per cent of all carcinomas. From 1905 to 1914 these percentages were 0.19 per cent and 2.36 per cent respectively. From 1915 to 1924 these corresponding figures were 0.47 per cent and 6.69 per cent respectively. Somewhat similar increases in the incidence of bronchogenic carcinoma have been reported by numerous others.<sup>1</sup> The relatively greater increase in the incidence of pulmonary carcinoma is shown by Rosahn's collected series of cases. Whereas the incidence of carcinoma in all autopsies increased from 10.27 per cent in the period 1910 to 1919 to 12 per cent in the period 1920 to 1928, the incidence of pulmonary carcinoma in all postmortem examinations increased from 0.44 per cent to 0.89 per cent in these respective periods. Thus, the incidence of carcinoma of the lung in all autopsies doubled in this period, whereas the increase in the incidence of all carcinoma in all autopsies was relatively slight. Similar figures were shown by the statistics from the Dresden City Hospital. Reinhard reported the autopsies in this institution from 1852 to 1856 and found that the percentage of pulmonary carcinomas in all autopsies was 0.057, 0.92 per cent of all carcinomas. During the period 1877 to 1894 Wolf found that the percentage of cancer of the lung in all autopsies had increased to 0.351. Rau reported the autopsies from 1909 to 1914, noting an incidence of pulmonary carcinoma of 2.72 per cent of all carcinomas and an incidence of 4.66 per cent in the series examined from 1914 to 1919. Thus, the incidence of carcinoma of the lung as based on all malignant tumors observed in postmortem examinations at the same institution had

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1. Berblinger; Biberfeld; Brandt; Ferenczy and Matolcsy; Hauf; Hueck; Junghanns; Kühn; Materna; Maxwell and Nicholson; Probst; Seyfarth S.; Simpson; Sonnenfeld; von Glahn; Wahl; Zalka.

increased fivefold during a sixty-seven year period. Olson, in reporting the cases of carcinoma of the lung from the Boston City Hospital, found that the incidence of pulmonary carcinoma increased annually from 7.5 per cent of all carcinomas in 1929 to 19.1 per cent in 1934. Matz found that in the autopsies performed in the Veterans' Bureau Hospital the incidence of pulmonary carcinoma increased from 6.4 per cent of all carcinomas for the years 1927 to 1931 to 15.8 per cent for the years 1932 to 1937. It is of interest, also, that in the last year, 1937, this incidence was 23.4 per cent. Pekelis noted an incidence of carcinoma of the lung of 0.87 per cent of all carcinomas for the years 1920 to 1924 and an incidence of 2.29 per cent from 1925 to 1929. Loizaga reported an incidence of carcinoma of the lung of 5.18 per cent of all carcinomas in the autopsies of the Institute of Pathological Anatomy of the Faculty of Ciencias Medicas of Buenos Aires, Argentina, during the period 1898 to 1917 and an incidence of 14.6 per cent during the years 1918 to 1937. The same author found that the incidence of pulmonary carcinoma in an autopsy series at the Francisco Janvier Hospital was 29.62 per cent of all carcinomas during the period 1927 to 1931 and 42.25 per cent from 1932 to 1937. Hoffman found that the incidence of carcinoma of the lung among all patients who die has increased. In 1914 this incidence showed that the number of cases of carcinoma of the lung was equivalent to 0.6 per cent per hundred thousand of population. In 1924 this increased to 1.6 per cent per hundred thousand of population; in 1925, to 1.7; in 1926, to 1.8, and in 1928, to 1.9. In this connection we have reviewed the mortality statistics on all persons in the United States who died of pulmonary malignant tumors during the period 1920 to 1936 inclusive. It was found that there was not only an actual increase in the number of deaths from this cause but an annual increase in the death rate per hundred thousand of population (fig. 1). Staehelin found that the percentage of carcinoma of the lung in all autopsies increased gradually from 0.2 during the period 1900 to 1911 to 0.67 in 1924. Barron, at the University of Minnesota, found no cases of carcinoma of the lung among 1,032 autopsies from 1899 to 1911. From 1912 to 1918 the incidence of carcinoma of the lung in all autopsies was 0.19 per cent, and from 1919 to 1921 this incidence had increased to 0.89 per cent. More recent data from this institution showed the increased incidence to have continued. Hruby and Sweany collected a series of 185,434 autopsies reported during the thirty-four year period 1897 to 1930 inclusive and found that the incidence of cancer of the lung increased more than did the incidence of cancer in general. The incidence of pulmonary carcinoma in the necropsies performed at the Charity Hospital in New Orleans has increased in the past seven years approximately five times. In 1931, among 635 necropsies there were 3 (0.47 per cent) carcinomas

of the lung. In the same period there were 15 (2.3 per cent) carcinomas of the stomach. In 1938, among 825 necropsies, there were 17 (2 per cent) carcinomas of the lung and 16 (1.9 per cent) carcinomas of the stomach. It is thus seen that in the Charity Hospital the relative incidence of carcinoma of the stomach has decreased but the incidence of carcinoma of the lung in patients coming to necropsy has increased approximately four times (fig. 2).

The cause of the increasing incidence of carcinoma of the lung is not definite. In fact, there are many who believe that the increase is only apparent and not actual. Fried stated the opinion that the increased occurrence of pulmonary carcinoma is due to improved clinical and

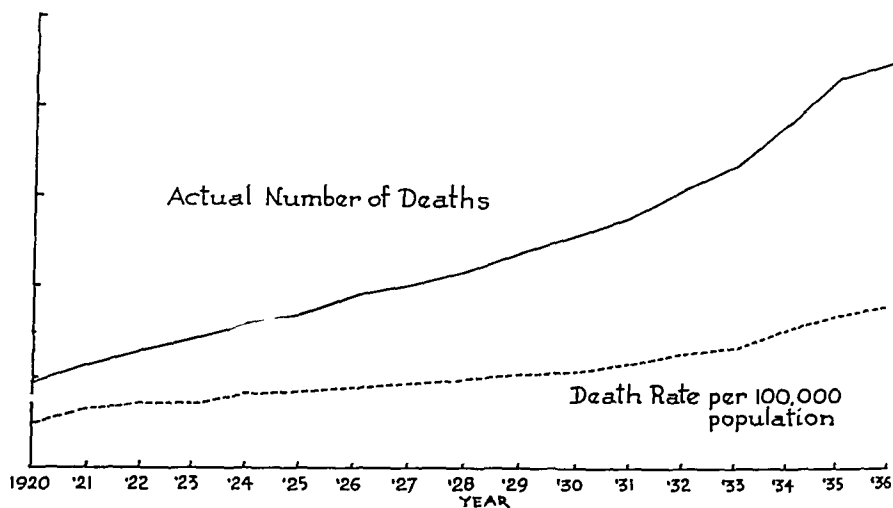


Fig. 1.—Graphic representation of the mortality from cancer of the lung in the United States according to vital statistics, showing not only an actual increase in the number of deaths but an annual increase in the death rate per hundred thousand of population. There was an increase in the actual number of deaths from 956 in 1920 to 4,648 in 1936 and in the death rate per hundred thousand of population from 1.1 in 1920 to 3.6 in 1936.

pathologic methods of diagnosis, increased attention to the condition permitting more frequent diagnoses. Whereas this might explain the increase in the incidence of pulmonary carcinoma seen and diagnosed clinically, it certainly cannot explain the definite increase in the necropsy series. An additional explanation given by Fried for the increase is that, owing to the increased life expectancy, more persons reach the "cancer age" than formerly. This undoubtedly may explain some of the increase in the incidence of pulmonary carcinoma, but it certainly cannot explain the disproportionate increase in carcinoma of the lung as compared with carcinoma elsewhere, which is exemplified by the statistics from the Charity Hospital and by those of Matz. Moreover, a review of the death

rates per hundred thousand of population of persons in the United States dying of malignant tumors of various organs, as shown by the mortality statistics of the bureau of census, reveals a relatively greater increase in

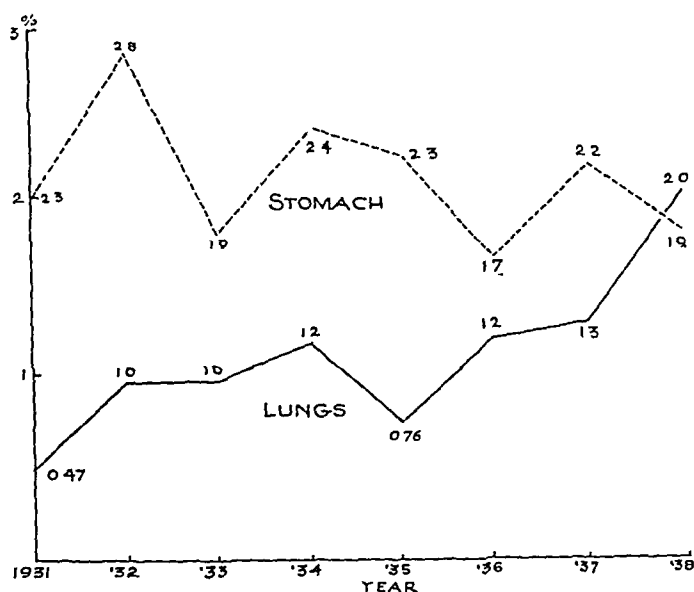


Fig. 2.—Graphic representation of the relative incidences of gastric and pulmonary cancer in necropsies performed at the Charity Hospital during the eight year period from 1931 to 1938 inclusive.

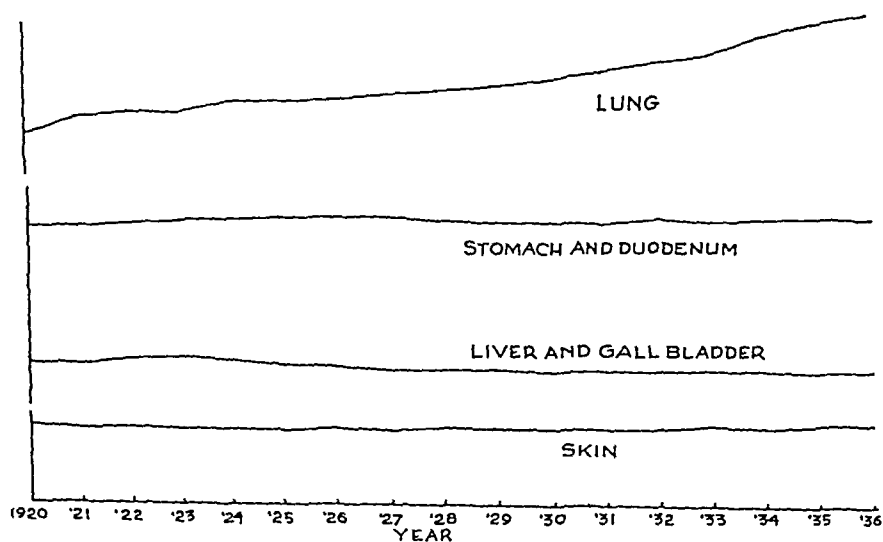


Fig. 3.—Graphic representation of the relative incidences of cancer of the lung and cancer of other organs based on mortality statistics for the United States during the seventeen year period from 1920 to 1936 inclusive.

the incidence of carcinoma of the lung (fig. 3). Whereas during the period 1920 to 1936 inclusive the incidence of carcinoma of the stomach



and duodenum, of the liver and gallbladder, of the uterus and of the skin showed little if any increase, the incidence of carcinoma of the lung showed a progressive rise (fig. 3).

From the foregoing statistics it is evident that pulmonary carcinoma is absolutely increasing and is becoming a significant problem in the treatment of cancer. It is of significance that in the necropsies performed during the past year at the Charity Hospital carcinoma of the lung occurred more frequently than did carcinoma of the stomach and that, whereas the incidence of carcinoma of the stomach has remained about the same for the past seven years, there has been a definite and progressive increase in the incidence of carcinoma of the lung. Of interest also in this regard is the report of Hirsche and Halpert, who found, in reviewing the necropsies performed at the department of pathology of Yale University during the period 1917 to 1934, that carcinoma of the lung was third in frequency, being preceded only by carcinoma of the stomach and carcinoma of the large bowel.

#### ETIOLOGIC CONSIDERATIONS

A number of theories have been advanced to explain the increase in pulmonary carcinoma. Winternitz, Wason and McNamara, because of the presence of metaplasia in the bronchial mucosa of persons dying from influenza, suggested that this change is a precancerous lesion. A similar suggestion was made previously by Askanazy, who found in 38 of 90 patients dying of influenza "the normal columnar epithelium of the bronchus to be replaced by stratified squamous epithelium or that there occurred a metaplasia (protoplasia) of the bronchial mucosa." Similarly, others<sup>2</sup> have suggested a possible relation between the influenzal epidemic of 1918 and the increase in pulmonary carcinoma. Bauer and Meyer were among the first to report cases of carcinoma of the lung following grip. Berblinger and more recently Oberndorfer concluded that "flu" is among the principal causes of cancer of the lung. On the other hand, Fried, in a series of 47 cases of carcinoma of the lung observed since 1918, had only 1 in which there was a history of influenza. He stated the belief that influenza plays little if any role in the causation of pulmonary carcinoma. Kikuth, in a series of 249 cases of carcinoma of the lung observed at autopsy, found that in only 21 was there a history of influenza. Koopmann, in a relatively large series of cases, found no evidence of metaplasia. In 139 necropsies studied by Simpson, only 5 of the patients had had influenza preceding cancer of the lung. Krompecher found no increase in cancer of the lung due to influenza. After carefully reviewing this question, Hueper concluded that there is no significant relation between influenza and bronchogenic carcinoma.

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2. Barron; Berblinger; Läsche; Mittasch; Moise; Schmidtman; Teutschlaender.

Other chronic specific and nonspecific pulmonary infections have also been cited as playing possible etiologic roles in the production of cancer of the lung. Of these, tuberculosis is probably the most frequently mentioned. Ewing stated that the tubercle bacillus is an "irritating" agent and one of the most important etiologic factors in bronchogenic carcinoma. Barron and Cherry also expressed the belief that tuberculosis plays a possible role in the production of these tumors. Of 31 patients reported on by Wolf, 14 had tuberculosis. Fried recently reported 13 cases in which carcinoma and tuberculosis coexisted. On the other hand, Rokitansky long ago emphasized the rare occurrence of cancer and tuberculosis in the same person at necropsy, an observation subsequently made by others.<sup>3</sup> Of significance in this regard is the report by Sison and Monserrat that in the Philippines the incidence of carcinoma of the lung is low and that of pulmonary tuberculosis high. In a series of 246 patients with carcinoma of the lung, Kikuth found only 22 with tuberculosis. Lóizaga and Vivoli found only 1 case of carcinoma of the lung in 2,400 autopsies on tuberculous patients. In a comparison of 886 persons with active tuberculosis and a similar group without tuberculous involvement, Pearl found the incidence of malignant tumors in the former group to be 1.2 per cent, and in the latter, 9.3 per cent. Pearl concluded that the rarity of the two lesions in the same person "is apparently due to a significant antagonism between the two pathologic phenomena which disappears when and if the tuberculous process retrogresses or heals, particularly by the fibrotic route." Similar observations were made by Carlson and Bell.

Syphilis has also been recorded as a possible factor.<sup>4</sup> Letulle observed syphilitic changes in 6 of 11 cases. Others have also observed the coexistence of these lesions.<sup>5</sup> However, there is insufficient evidence at present for considering syphilis of the lung a carcinogenic potentiality.

Of the nonspecific chronic inflammatory pulmonary lesions, bronchiectasis and chronic bronchitis have been most frequently cited as possible etiologic factors in bronchogenic carcinoma. Frommel found that chronic bronchitis, bronchiectasis and emphysema were present in 29 of 41 cases of cancer of the lung. Klotz reported a case in which a tumor developed in the bronchiectatic cavity in a patient who had suffered with bilateral bronchiectasis for fifteen years. The clinical as well as postmortem observation of chronic pulmonary inflammatory lesions in cases of pulmonary cancer is not infrequent.<sup>6</sup> The metaplastic changes consequent to injury of the epithelium by such chronic inflammatory lesions form

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3. Albrecht; Grove and Kramer; Lóizaga and Vivoli; Lubarsch; Reinhardt.

4. Simpson; Ziemssen.

5. Bonnamour and others; Brouardel and others; Martin and Colrat; Popper; Rouslacroix and Blanc.

6. Fried; Hunt; Klotz; Läsche; Simpson.

the basis for their consideration as a possible carcinogenic factor.<sup>7</sup> Metaplasia in the presence of bronchiectasis has been observed in laboratory rats.<sup>8</sup>

The inhalation of irritating gases, such as war gas, exhaust gas of combustion motors and gases arising from tarred roads, has been suggested as an etiologic factor in the production of pulmonary carcinoma. Kawahata observed 21 cases of carcinoma of the lung in six years among workmen employed in an illuminating gas generator and consequently exposed to dust and hot gases containing tar. Experimentally, it is possible to produce carcinoma of the lung in animals by the use of tar applied to the surface of the animal. Möller painted the backs of young rabbits with tar and observed that a fairly high percentage of the animals had bronchogenic carcinoma. Similar results were observed by Murphy and Sturm. Seelig and Benignus found that, whereas only 1 of their control animals had carcinoma of the lung, 8 of 100 mice exposed to coal soot had such lesions. Kimura by means of intrabronchial inhalation of coal tar produced in the lung of a rabbit and a guinea pig small circumscribed nodular neoplasms. Smith observed no pulmonary tumors in 20 mice exposed to coal tar fumes, 1 carcinoma in 26 mice exposed to the exhaust of an automobile and 1 pulmonary neoplasm in 29 mice painted with gasoline. He concluded that this proportion was not markedly greater than the spontaneous occurrence of carcinoma of the lung in such animals. Bonne performed experiments on mice by injecting intratracheally dried pulverized tar-acacia emulsion and found no significant increase in pulmonary tumors over control animals. Similarly, Campbell concluded that exposure of mice to exhaust gas from internal combustion engines has little effect on the incidence of primary tumors of the lung as compared with that among controls. Hampeln stated the belief that there is a definite relation to the increased production of smoke and dust in large cities, in that these substances by constant inhalations produce a chronic irritation of the bronchial and pulmonary epithelium, increasing the frequency of carcinoma of the lung. Staehelin also stated the opinion that the inhalation of dust containing chemical substances which possess a specific carcinogenic agent is responsible for pulmonary carcinoma. He stated the belief that the small tar and dust particles in the dust of tarred or oiled roads and the oxidation products of gasoline and benzene inhaled daily in large amounts are causative factors for the increase. An increased incidence in carcinoma of the lung among open air workers exposed to road dusts was observed by Kennaway and Kennaway. Heilman also stated the opinion that the inhalation of gasoline and tar products originating from the use of auto-

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7. Bonner; Goltz: Siegmund.

8. Passey, Leese and Knox.

mobiles and tarred roads is responsible for the production of pulmonary carcinoma. On the other hand, Davidoff and Uspensky stated that in Russia, where there are few automobiles and few, if any, of the roads are painted with tar, there has been a definite increase in carcinoma of the lung in the past ten years. Similar observations have been made by Boyd in Canada and by Husted and Biilmann in Denmark. Passey and Holmes contended that in Great Britain the increasing incidence in pulmonary malignant tumor began before the tarring of roads. Similarly, Konrad and Franke observed that the condition is increasing in the town of Riga, where there has been no increase in the tarring of roads or in the number of motor cars. As a result of his investigations of the tar content of dust raised from tarred streets by motor vehicles, Lehmann concluded that this factor is of little etiologic significance. Probst made a thorough review of this subject and came to a similar conclusion. These facts would certainly tend to disprove the importance of the inhalation of tar and benzene products in the production of pulmonary carcinoma.

It has been known for a long time that the inhalation of radioactive substances is responsible for the development of pulmonary carcinoma. This is demonstrated conclusively by a high incidence of carcinoma among the workers in the Schneeberg mines, first emphasized by Arnstein. Rostoksi, Saupe and Schmorl found that 62 per cent of workers in the Schneeberg mines who were followed until death died of primary pulmonary carcinoma. A recent report of studies<sup>8a</sup> on the Schneeberg miners conducted by the government committee for prevention of cancer stated that these malignant tumors are considered due to radioactive emanations. Döhnert kept 48 mice in the Schneeberg mines for periods ranging from two hundred to three hundred and seventy days, and of 26 submitted to microscopic examination 7 were found to have neoplasms, 2 of which were in the lung. He concluded that these tumors were caused by the radium contained in the air. In addition to being radioactive, the dust contains a high content of arsenic and cobalt.<sup>9</sup> Similar observations were made by Pirchan and Sikl, who studied the pitchblende mines of Joachimsthal, which is across the mountains from Schneeberg. The latter authors found radium emanation in the air of Jáchymov pits to be as high as 50 maché units. Peller found that during the years 1929 to 1938, 89 Joachimsthal miners died, 6 of whom were examined post mortem. Of these, 47 (52.8 per cent) died of cancer, 42 of whom had primary tumors in the lung. Peller stated the opinion that the high incidence of primary pulmonary cancers among these miners is due to the radioactive factor in the mines. Although the presence of the dust

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8a. Brandt.

9. Schmorl; Uhlig.

alone might be responsible for the development of pulmonary carcinoma, the investigative work of Willis and Brutsaert would tend to disprove this, as would the fact that pulmonary carcinoma is not as frequently found in other miners who have pneumoconiosis as do those in the Schneeberg mines. Willis and Brutsaert were able to produce tumor-like structures in the lungs of guinea pigs exposed to silica (silicon dioxide) dust, but there was no evidence of carcinoma developing. Moreover, experimental attempts to produce malignant lesions in the lungs of mice by the inhalation of Schneeberg drill dust were unsuccessful.<sup>10</sup>

In an attempt to determine the significance of occupation in the development of cancer of the lung, Brockbank analyzed 898 cases collected from the literature and found that, whereas no single occupation was prominent, the laboring classes predominated. The etiologic significance of pneumoconiosis and silicosis in primary pulmonary carcinoma has recently received careful scrutiny. A number of cases have been reported from various parts of the world.<sup>11</sup> Charr observed that of 36 patients with anthraco-silicosis who came to autopsy, 4 had primary carcinoma of the lung. Anderson and Dible, on the basis of studies of the silica content and histologic evidence of pneumoconiosis in 70 patients with and 50 without carcinoma of the lung, concluded that silicosis plays an important etiologic role. Klotz reported that of 50 patients with silicosis coming to autopsy during the period 1925 to 1936 there were 4 (8 per cent) with bronchogenic carcinoma; in 4,500 necropsies during this same period there were only 53 (1.18 per cent) primary pulmonary malignant tumors. Similarly, Lynch and Smith found that the incidence of carcinoma of the lung in a large series of consecutive necropsies was 0.21 per cent, in contrast to an incidence of 6 per cent in a series of cases of asbestosis. On the other hand, a recent survey of the literature in this regard by Vorwald and Karr has led them to the conclusion that "inhaled dusts except those containing recognized carcinogenic substances such as radium and tar, cannot in general be considered as etiological factors in the development of primary pulmonary carcinoma." Of particular interest is the report of the Miner's Phthisis Medical Bureau in South Africa. Whereas in an autopsy series of 1,438 European miners with silicosis there were 10 (0.7 per cent) with carcinoma of the lung, of 1,679 European miners without silicosis there were 12 (0.71 per cent) with carcinoma of the lung. Thus, it can be readily observed from these conflicting reports that the etiologic role

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10. Rostoski, Saupe and Schmorl.

11. Allen; Charr; Cramer; Dible; Dreyfus; Egbert and Gerger; Fine and Jaso; Gloyne; Horning; Klotz; Lynch and Smith; Maxwell; Middleton; Nordmann; Saupe; Sladden; Stewart and Faulds; Sweany and others.

of pneumoconiosis and silicosis in the causation of bronchogenic carcinoma is not definitely established.

In a previous publication (*Surg., Gynec. & Obst.* 68: 435, 1939) we called attention to the possible etiologic relation between the increase in smoking, with the universal custom of inhaling, and the increase in pulmonary carcinoma. The inhalation of smoke constantly repeated over a long period produces a chronic irritation of the bronchial mucosa, as is evinced by the characteristically associated cough. As early as 1923, Fahr stated that in his opinion the increase in the incidence of pulmonary carcinoma was due to the increased incidence of cigaret smoking. Lickint also expressed the opinion that the inhalation of tobacco smoke is a responsible factor in the increase of bronchogenic carcinoma and that such carcinoma in many cases can be prevented by abstinence from smoking, particularly by patients belonging to families known to have a high cancer incidence. Tylecote stated: "In almost every case I have seen and known of the patient has been a regular smoker, generally of cigarets." McNally expressed the opinion that the tar of cigaret smoke may account for the recorded increase of cancer of the lung. Mertens has also expressed this view. Bogen and Loomis stated that the only woman with cancer of the lung on whom autopsy was done at the Olive View Sanatorium had smoked cigarets excessively for more than fifteen years.

Experimentally, the irritating carcinogenic effects of tobacco have been demonstrated repeatedly.<sup>12</sup> There are a number of substances contained in tobacco which may act as irritants. Of these, nicotine has been chiefly considered by most investigators. Being an alkaline substance, McNally stated, "its continual contact with the delicate cells of the lungs during the inhalation of smoke must cause irritation." The nicotine contained in the aspirated smoke may reach high proportions. Asherson stated that the nicotine content of the smoke of one cigaret may be 6 to 8 mg. According to Winterstein and Aronson, from 13 per cent to 15 per cent of the nicotine content of cigarets is absorbed.

In addition to nicotine, there are other substances in tobacco, such as pyridine bases, phenolic bodies, ammonia and certain hygroscopic agents, which have been shown to act as irritants. Stoeber and Wacker produced epithelial proliferation in animals by pyridine, and Hamilton stated that pyridine produces lesions on the skin similar to those observed in patients handling tarry substances. McNally stated the opinion that in addition to nicotine the tarry material separating from the smoke has a significant irritant action. He found that from 6.5 to 11.5 per cent of

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12. Boehncke; Leitch; Lickint; Lu-Fu-hua; Morpurgo; Philippon; Roffo; Roffo and Bisi; Wacker and Schminke.

this residue may be absorbed or retained in the body. Some hygroscopic agent is usually added to cigaret tobacco for the purpose of assuring a satisfactory moisture content and to act as a binder. Glycerin and diethylene glycol are most commonly used. Clinical and experimental investigations have demonstrated convincingly that these substances increase the irritant effect of tobacco smoke. Whereas some observers<sup>13</sup> are of the opinion that cigalets treated with diethylene glycol are less irritating than those treated with glycerin, Haag concluded from his experimental investigations that there are "no differences in the irritating properties of the two types of cigalets.

Roffo stated the conviction, on the basis of his clinical observations of 78,000 patients treated in the University Institute for Experimental Medicine and for the Study of the Treatment of Cancer in Buenos Aires, that tobacco is the most important factor in determining the localization of cancer. He concluded as a result of his investigative work that the carcinogenic agent in tobacco responsible for the development of pulmonary carcinoma is not nicotine but tobacco tar, which is produced as a result of the burning of the tobacco. Roffo found that the carcinogenic effects of various tobaccos vary considerably and that the experimental production of tumors in rabbits with tar obtained from black Kentucky tobacco is as easy as with coal tar. With both of these substances, when the tar was applied to the surface of the ear of the rabbit, a tumor developed in 100 per cent of cases. Whereas Dolley and Jones in a recent publication cited Hoffman as stating that he was unable to find a single case of carcinoma of the lung attributable to nicotine, we can find no evidence of this statement in Hoffman's publication. On the contrary, Hoffman, from his statistical investigations, concluded that smoking probably plays a definite etiologic role. In a subsequent article, Hoffman stated: "They (statistics) undoubtedly are indicative of the greater liability to certain forms of cancer among those who have acquired heavy smoking habits than among those who indulge normally. Personally, I am strongly of the opinion that a relation between the increase in smoking habits and cancer of the lung may be safely assumed to exist." In conclusion he stated: "Smoking habits unquestionably increase the liability to cancer of the mouth, the throat, the esophagus, the larynx, and the lung. The change in the cancer death rate during recent years has not, however, been at all disproportionate to the enormous increase in the cigarette smoking habit which has replaced the older method of smoking, unquestionably more injurious than smoking of cigarettes. The increase of cancer of the lung observed in this and many other countries is in all probability to a certain extent directly

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13. Flinn; Mulinos and Osborne; Wallace and others.

traceable to the common practice of cigarette smoking and inhalation of cigarette smoke. The latter factors unquestionably increase the danger of cancer development."

It is our definite conviction that the increase in the incidence of pulmonary carcinoma is due largely to the increase in smoking, particularly cigaret smoking, which is universally associated with inhalation. Every one of our patients, with the exception of 2 women, was an excessive smoker. Of particular interest in this connection is the comparison of the death rate per hundred thousand of population from cancer of the lung with the production of tobacco and automobiles in the United States during the seventeen year period 1920 to 1936 inclusive. It may be

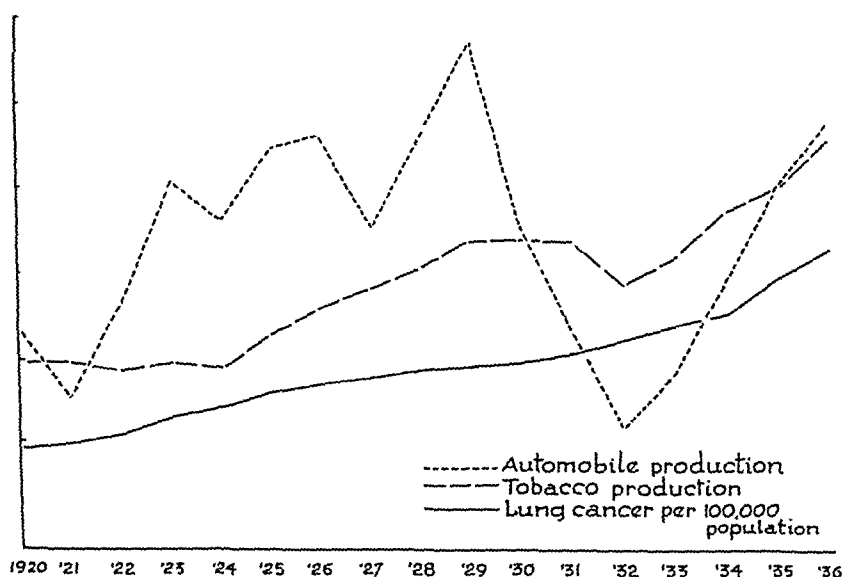


Fig. 4.—Graphic representation of a correlation of the death rate per hundred thousand of population from cancer of the lung with the production of tobacco and automobiles in the United States during the seventeen year period from 1920 to 1936 inclusive.

observed from a graphic representation of these incidences that, whereas there is no significant relation between the production of automobiles and cancer of the lung, there is an obvious parallelism between the increased production of tobacco and carcinoma of the lung (fig. 4).

The etiologic role played by trauma in carcinoma of the lung is of doubtful significance (Knox). Isolated cases of the development of pulmonary carcinoma following severe trauma to the chest have been reported.<sup>14</sup> Obviously the fact that an early neoplasm existed prior to the trauma cannot be excluded.

14. Aufrecht; Georgi; Gomez; Handford; Hedinger; Hinterstoisser; Luckow; Schöppler; Scott and Forman; Wells and Cannon.



*Sex.*—It has long been recognized that pulmonary carcinoma occurs principally in the male sex. There has been an apparent increase in the number of male patients in relatively recent series. In Adler's<sup>15</sup> series, reported in 1912, approximately 70 per cent of the tumors occurred in males. More recently the incidence of involvement of the male has become even greater. In collected series both Breckwoldt and Egenolf found the incidence in males to be 74 per cent, and Simons observed that males predominated in the ratio of 4 to 1. The increase in pulmonary carcinoma in the male sex has been thought to be due to the previously greater prevalence of smoking among the sex (Ferrari). Undoubtedly, if smoking plays a role, which we believe it does, the relative percentages for men and women will become more equalized because of the recently increased number of women who smoke. In a collected series<sup>15</sup> of 8,575 cases in which the sex was stated (fig. 5) there were

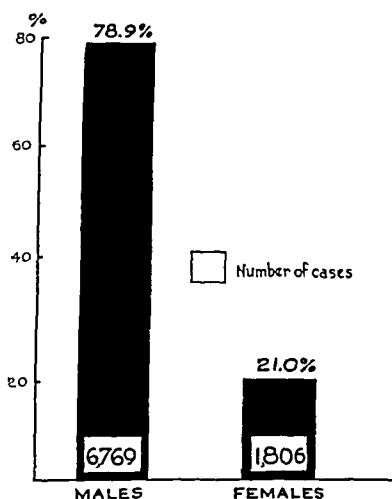


Fig. 5.—Graphic representation of the sex incidence of cancer of the lung, based on 8,575 collected cases.

15. Adler; Andrus; Arkin and Wagner; Beal; Bejach; Beller; Berblinger; Biberfeld; Bilz; Bonser; Brandt; von Braunbehrens; Breckwoldt; Briese; Brines and Kenning; Brockbank; D'Aunoy, Pearson and Halpert; de la Camp; de Vries; Duguid; Dynkin; Egenolf; El-Gazayerli; Eloesser; Farrell; Feilchenfeld; Fenger and Petter; Ferenczy and Matolcsy; Fried; Frissell and Knox; Fuchs; Funk; Geschickter and Denison; Graham; Singer and Ballon; Grove and Kramer; Haberfeld; Haintz; Hamman; Hauf; Herlant; Heyman; Hoffman; Holzer; Howes and Schenck; Hruby and Sweany; Huguenin; Hunt; Jackson and Konzelmann; Jaffé; Junghanns; Karrenstein; Katz; Kaufmann; Kikuth; Klotz; Koletsky; Kraft; Krasting; Krompecher; Kuhn; Lipschitz; Lloyd; Lóizaga; Lubarsch; Lumsden; Marchesani; Materna; Matheson; Maxwell and Nicholson; Menne, Bisailon and Robertson; Miller and Jones; Moise; Moses; Müser; Nolan; Olson; Ormerod; Overholt and Rumel; Parish; Passler; Peet; Pierce and Ingersoll; Probst; Puente Duany and his associates; Rau; Ravdin; Redlich; Reinhard;

6,769 males (78.9 per cent) and 1,806 females (21 per cent). It is thus seen that approximately 3 of every 4 carcinomas of the lung affect the male.

*Age.*—As might be expected, carcinoma of the lung usually occurs in older persons. Brunn found that 62 per cent of 576 occurred in persons between 40 and 60 years of age. Weller found that the greatest incidence is in the sixth and seventh decades. According to Olson, in 73.8 per cent of his cases of carcinoma of the lung the tumor occurred in the fifth, sixth and seventh decades. Breckwoldt, in a large series of collected cases, found the most frequent occurrence between the ages of 50 and 70 years. Fischer, in a series of 1,888 collected cases, found that one third of the tumors occurred in the fifth decade, one third after the age of 60

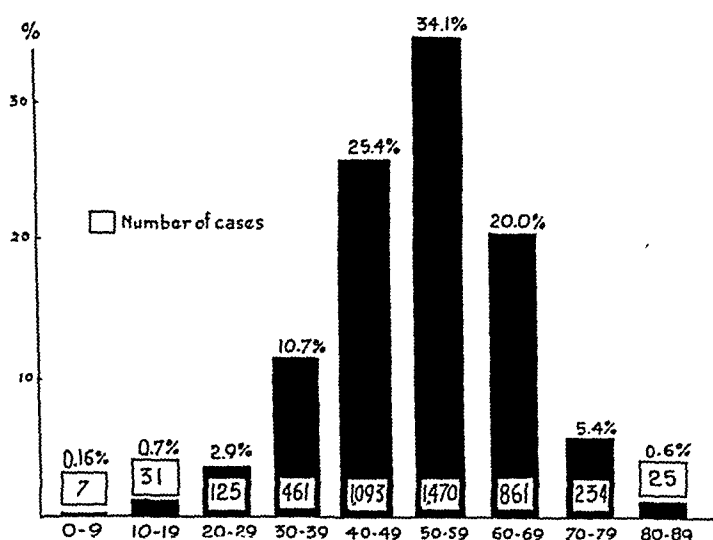


Fig. 6.—Graphic representation of the age incidence of cancer of the lung, based on 4,307 collected cases.

and 13 per cent under the age of 40. There were 4 tumors in children under 10. Simons, in a collected series of over 5,000 cases, found that four fifths of the tumors occurred between the ages of 40 and 70. Schwyter and Beardsley each reported observation of the tumor in a 16 month old child. However, the youngest patient whose case has been recorded is probably that of Weill-Hallé and his associates, who reported on a primary carcinoma of the lung in a child 1 year of age. Other patients under 10 years of age have also been reported on.<sup>16</sup> The oldest patient, 91 years of age, was probably Frommel's. In a series

Riechelmann; Rice; Robet; Rogers; Rokenstone and Schwartz; Sachs; Sampson; Schamoni; Schlesinger; Schmoller; Schwalbe; Schrt; Seyfarth; Sherman; Sierra; Simpson; Strnad; Vinson; Wasch and Epstein; Watsuji; Winternitz; Wolf; Zalka.  
16. Gould; Lereboullet and others; Lóizaga; Nuschler.

of 4,307 collected cases<sup>17</sup> arranged according to decades, the following results were found: first decade, 0.16 per cent; second decade, 0.7 per cent; third decade, 2.9 per cent; fourth decade, 10.7 per cent; fifth decade, 25.4 per cent; sixth decade, 34.1 per cent; seventh decade, 20 per cent; eighth decade, 5.4 per cent, and ninth decade, 0.58 per cent (fig. 6). It is thus seen that well over half the patients are between the ages of 40 and 60 (59.5 per cent) and approximately four fifths are between the ages of 40 and 70. It is of significance, however, that 10.7 per cent were between the ages of 30 and 40 and that approximately 40 per cent were under 50 years of age. These

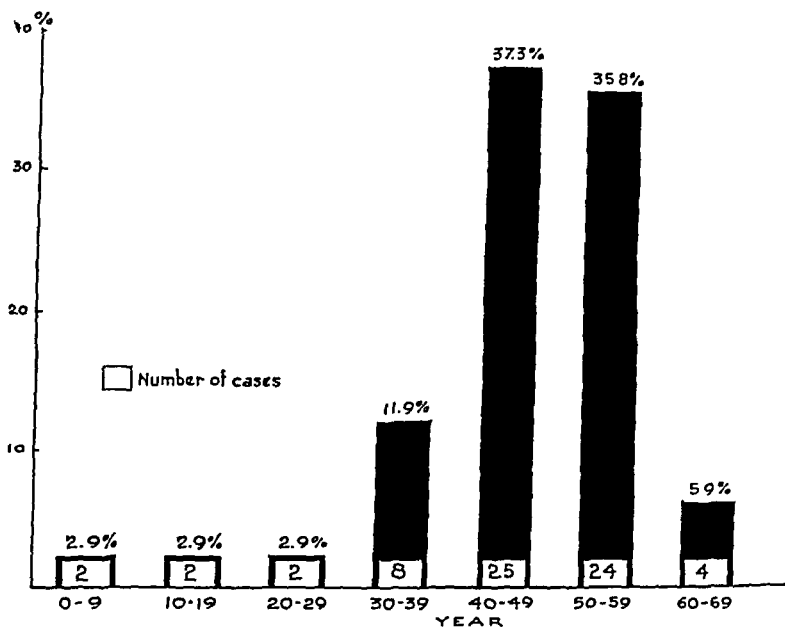


Fig. 7.—Graphic representation of the age incidence in the collected cases of pneumonectomy for cancer of the lung.

figures are of interest when compared with the age of patients on whom total pneumonectomies have been done. In a collected series<sup>18</sup> of 116

17. Adler; Arkin and Wagner; Baudin and Evans; Beardsley; Breckwoldt; Biberfeld; Briese; Brines and Kenning; Brockbank; Bryan; D'Aunoy and his associates; Duguid; Egenolf; El-Gazayerli; Eloesser; Farrell; Ferenczy and Matolcsy; Frissell and Knox; von Glahn; Gould; Grove and Kramer; Graham and his associates; Hauf; Holzer; Huguenin; Hunt; Jackson and Konzelmann; Jaffé; Karrenstein; Kikuth; Koletsky; Kramer and Som; Kuhn; Lereboullet and his associates; Lóizaga; Matz; Maxwell and Nicholson; Moise; Mosto and Polak; Nuschler; Olson; Pierce and Ingersoll; Probst; Rogers; Schlesinger; Schwyster; Strada; Strnad; Vinson; Weill-Hallé and his associates; Wahl; Zalka.

18. Adams; Alexander; Allison and Stanbury; Arce; Archibald; Behrend and Behrend; Bigger; Churchill; Crafoord; Dolley and Jones; Duval and Monad; Edwards; Finochietto and Aquilar; Flick and Gibbon; Freedlander; Frissell and

cases, including 15 of our own, the ages were given in 67. For these 67 cases the age incidence was as follows: 2 patients (2.9 per cent) were in the first decade; 2 (2.9 per cent) were in the second decade; 2 (2.9 per cent) were in the third decade; 8 (11.9 per cent) were in the fourth decade; 25 (37.3 per cent) were in the fifth decade; 24 (35.8 per cent) were in the sixth decade, and 4 (5.9 per cent) were in the seventh decade (fig. 7). It is significant that 57 per cent of these patients were under 50 years of age, as contrasted with 48 per cent of the entire group. This difference is undoubtedly due to the fact that the younger patients were chosen for pneumonectomies, whereas the older patients were not considered suitable for the procedure. Undoubtedly, many of the older patients will be given the advantage of a pneumonectomy in subsequent series, since the safety of this procedure has been demonstrated. The incidence for the entire group of collected cases of carcinoma was four times greater in patients above 60 years of age than in the group subjected to total pneumonectomy. This difference is perfectly obvious, for the reasons previously given.

*Pathologic Picture.*—Carcinoma of the lung is invariably bronchogenic in origin. Until recently, however, there has been some controversy concerning this fact, as it had been thought that probably some of the carcinomas originate from the parenchyma of the lung and are not bronchogenic. At present it is generally accepted that all pulmonary neoplasms originate from the bronchial mucosa. As regards the location of primary neoplasms of the lung, the right side is involved more frequently than the left. In Fischer's series of 3,735 cases of pulmonary carcinoma the right side was involved in 53 per cent and the left in 45 per cent, and in 2 per cent the lesion was bilateral. In 4,732 cases which we have collected from the literature,<sup>19</sup> there were 2,761 (58.3 per cent) tumors involving the right lung and 1,971 (41.6 per cent) involving the left lung (fig. 8). In 784 of Fischer's cases in which the location according to the bronchus was designated, the findings were as follows: the main bronchus of the right lung was involved in 142; the main bronchus of the left lung, in 115; the bronchus of the upper lobe of the right lung, in 148; the bronchus of the upper lobe of the left lung, in 130; the bronchus of the lower lobe of the right lung,

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Knox; Graham; Graham and Singer; Haight; Hinz; Holst; Ivanissevich and Ferrari; Kummel; Lambret; Lilienthal; Lyle; Matson and others; Maurer; Meyer; Monad; Overholt; Overholt and Rumel; Rienhoff; Santy and others.

19. Adler; Bejach; Biberfeld; Bilz; von Braunbehrens; Breckwoldt; Briese; Brines and Kenning; Bryan; D'Aunoy and his associates; Egenolf; Eloesser; Ferenczy and Matolcsy; Fried; Frissell and Knox; Geschickter and Denison; Hauf; Herlant; Hochberg and Lederer; Hruby and Sweany; Jaffé; Kerrenstein; Kikuth; Koletsky; Kramer and Som; Kuhn; Lóizaga; Lumsden; Manges; Marchesani; Maxwell and Nicholson; Miller and Jones; Neely; Ormerod; Parish; Petzold; Probst; Rau; Redlich; Rice; Rogers; Sachs; Simpson; Strnad; Vinson; Wahl; Wasch and Epstein; Wolf.

in 129; the bronchus of the lower lobe of the left lung, in 105, and the bronchus of the middle lobe, in 15. Similar results, particularly as regards involvement of the upper lobe of the right lung, were reported by Breckwoldt and by Kikuth. Most pulmonary neoplasms are located centrally, that is, of hilar origin. According to Boyd, 90 per cent of these neoplasms are in the region of the hilus. In Frissell and Knox's series the incidence of hilar carcinomas was not as high, being only 49.7 per cent; 17.8 per cent involved the parenchyma and were of the nodular variety; 6.5 per cent were peripheral; 23.9 per cent were diffuse, and 2.1 per cent were bilateral miliary. According to Edwards, about 80 per cent of carcinomas of the lung occur in the larger lobe or bronchi or near the origin of the secondary bronchi and only 20 per cent in the peripheral bronchioles. Weller and Koletsky found that the lesions were hilar in 90 per cent and 86.6 per cent, respectively, of the cases they studied.

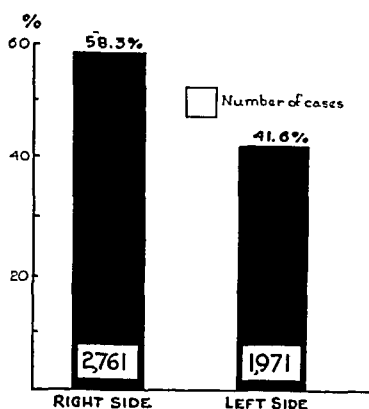


Fig. 8.—Graphic representation of the location of cancer of the lung, based on 4,732 collected cases.

*Microscopic Pathologic Appearance.*—There have been numerous classifications, usually based on the macroscopic or the morphologic appearance of the tumor.<sup>20</sup> Most frequently the classification used has been squamous cell carcinoma, small cell or undifferentiated cell carcinoma (oat cell carcinoma) and endocarcinoma. However, the classification which seems most logical to us is that proposed by Halpert, which we discussed in detail in our previous publication. This classification is based on the development of the cells lining the bronchi and adequately explains the histologic structure of all primary pulmonary carcinomas. Normally, the cells lining the mucous membrane of the bronchial tree represent varying degrees of differentiation and specialization of the original entodermal cells.

20. Aschoff; Barron; Breckwoldt; Briese; Eismayer; Fabris; Feyrter; Fishberg; Fried; Huguenin; Kaufmann; Marchesani; Meyer; Moise; Rabin and Neuho; Weller.

Apparently the undifferentiated entodermal ancestor cell is capable of developing into ciliated cylindrical epithelium, goblet cells, cuboidal cells, arranged into acinar and tubular structures producing a serous or mucous secretion, indifferent cells, lining the ducts of these glands, and into another kind of cuboidal or low cuboidal cells without cilia which line parts of the terminal bronchioles. In addition to the variety of cells just enumerated there are, beneath the ciliated cylindrical and goblet cells, a varying number of other epithelial cells which, like the basal cells in the epidermis, are lined up along the border toward the tunica propria. They are the cells from which the single layer of ciliated cylindrical and goblet cells are replenished. These cells, which may be called "reserve cells," are the parent cells of the ciliated, cylindrical, and goblet cells. In addition they naturally also possess the qualities of their ancestor cells in that they may differentiate into any kind of epithelium that an entodermal cell is capable of producing.

According to Halpert, carcinomas of the lung originate from these "reserve cells" by atypical proliferation.

These malignant growths may, therefore, be classified into three types, depending on the embryologic direction of growth: (1) "reserve cell" carcinoma, (2) cylindric cell carcinoma and (3) squamous cell carcinoma. This conception of the embryologic development of carcinomas is graphically illustrated by the development of the cells of the bronchial mucosa from a primitive entodermal cell. The "reserve cell" carcinomas consist of round, elongated or polygonal cells growing in solid masses and forming no particular structure. Characteristically they have a palisade arrangement of the peripheral cells. The cylindric cell carcinomas are composed of cuboidal or columnar cells forming tubular or acinar structures or are mounted on delicate connective tissue stalks in a papillary arrangement. The squamous cell carcinomas have a tendency toward keratinization or toward pearl formation with central keratinization.

Metastases from primary malignant tumors of the lung extend, as do those from malignant tumors elsewhere, in three ways: (1) by direct extension, (2) through the lymphatics and (3) through the blood stream. A fourth method of extension is "bronchial embolism." This has been described by Lumsden as surface spread. This method of extension has been insufficiently realized in the past but is, we believe, an important method of extension and is responsible in many instances for the peripheral involvement of the lung in those cases in which the primary lesion originates proximally (fig. 11). As might be imagined, the most frequent sites of metastatic involvement are the regional lymph nodes and the bronchial nodes. Next to the regional lymph nodes, the liver occupies first place in point of involvement. Kikuth stated that the regional lymph nodes are involved in practically all the cases. In Miller and Jones's series of 808 collected cases the liver was involved in 248 (30.7 per cent). In Koletsky's series of cases the tracheobronchial lymph nodes were involved in every instance, and the liver was involved in 40 per cent

of the cases. In Olson's series of cases the tracheobronchial lymph nodes were involved in 86 per cent and the liver in 35.8 per cent. It is of interest that the adrenals follow next in frequency in both of these series of cases, i. e., 38 per cent and 25.3 per cent respectively. King, in

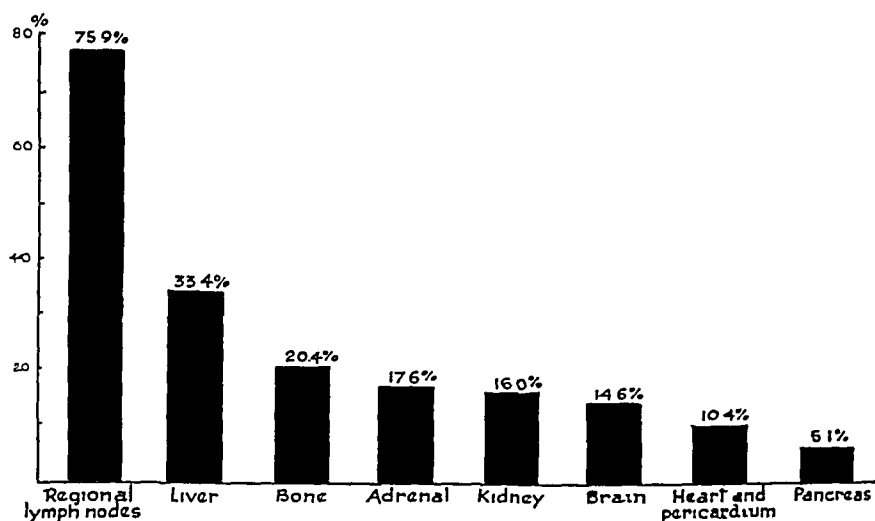


Fig. 9.—Graphic representation of the incidence of metastasis of cancer of the lung to various organs, based on 2,579 collected cases.

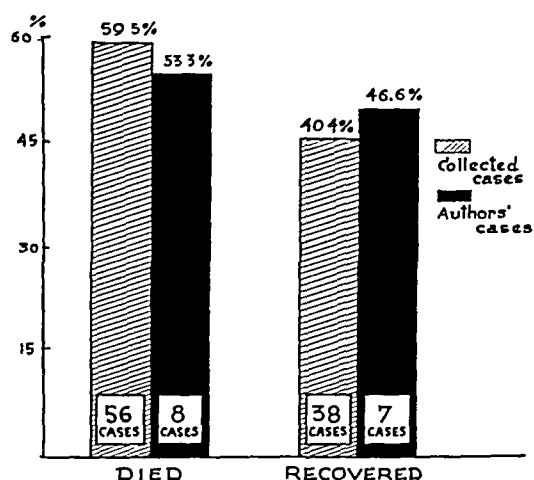


Fig. 10.—Graphic representation of the results in the collected cases of pneumonectomy and in our own.

a series of 72 autopsy cases, found that the bronchial lymph nodes were involved in one-half the cases, the adrenals and liver in one third of the cases, the bone and brain in one fifth of the cases, and the kidneys in one sixth of the cases. Lumsden observed 31 of 36 patients with metastases to the regional lymph nodes in a series. Frissell and Knox found

that in 97.4 per cent of their cases there was extension of the tumor to the regional lymph nodes. In a series of 2,579 collected cases,<sup>21</sup> the regional lymph nodes were involved in 75.9 per cent and the liver in 33.4 per cent (fig. 9). It is interesting in this connection that in a series of 808 collected cases, presented by Miller and Jones, the lymph nodes were involved in only 245 (30 per cent). The next most frequent sites of metastasis in the collected series<sup>5</sup> were as follows: bone, 20.4 per cent; adrenals, 17.6 per cent; kidney, 16 per cent; brain, 14.6 per cent; heart and pericardium, 10.4 per cent, and pancreas, 5.1 per cent (fig. 9). Involvement of the central nervous system is to be expected, because of the frequent association of lesions of the respiratory tract and lesions of the central nervous system. It is a well known fact that patients with



Fig. 11.—Photograph of the left lung removed at operation, showing a carcinoma originating in the upper lobe, with intrabronchial extension of the lesion.

suppurative disease of the lung are particularly likely to have a metastatic process in the brain. This is corroborated by the reported statistics.<sup>22</sup> Dosquet found that of 105 cases of carcinoma of the lung, there were metastases to the central nervous system in 33. In 22 of Olsen's cases in which the skull was opened, involvement of the cerebrum and cerebellum was observed in 36.3 per cent. Seyfarth found that of 309 cases, there were metastases to the central nervous system in 30.

21. Adler; Arkin and Wagner; Boyd; Briese; D'Aunoy and his associates; Dosquet; Eloesser; Ferenczy and Matolcsy; Fried; Frissell and Knox; von Glahn; Grove and Kramer; Halpert; Jaffé; Karrenstein; Kikuth; King; Klotz; Koletsky; Krompecher; Lumsden; Olson; Probst; Seyfarth; Simpson; Tuttle and Womack; Wahl; Zalka.

22. Craig, Wollman and Kernohan.



Simpson found that of 139 cases, there were metastases to the central nervous system in 19. Fried found that of 47 cases, there were metastases to the central nervous system in 16.

Although such high incidences of metastasis would indicate that the surgical treatment of pulmonary neoplasm is relatively hopeless, it should be realized that these figures are based on autopsy cases in which the tumors obviously were advanced. The fact that in approximately 70 per cent of cases the metastases were limited to the regional lymph nodes makes the prognosis as regards the surgical treatment much better. The fact that metastases do occur most frequently to the regional lymph nodes is significant, because in the surgical extirpation of a malignant lesion of the lung it is as important to remove the regional lymph nodes together with the primary focus as it is to do an axillary dissection for lesions of the breast. Only in this way can a radical operation be performed and the hope of a cure be obtained.

#### SYMPTOMS

Unfortunately, there are no characteristic symptoms of bronchial carcinoma. The onset of the condition is usually insidious, and the symptoms are disregarded because they are attributed to other causes, particularly to smoking. Hochberg and Lederer stated: "At present when cough seems to be habitual with the average person, every patient with a cough cannot be looked upon with suspicion as having neoplasm of the lung." It is unfortunate that the adult population is suffering with habitual cough, which is undoubtedly due to the ubiquitous use of tobacco. The fact remains that the most frequent symptom of bronchogenic carcinoma is cough. Brunn and Simons found cough to occur in 65 per cent and 72 per cent in their respective collected series. In Brines and Kennings' series of cases, cough was present in 87 per cent. In Frissell and Knox's series of cases it was present in 91 per cent and was the first symptom in 23.8 per cent. In all of our cases cough was a prominent manifestation, although in many it was considered by the patient to be of no consequence because of the fact that it had been present for some time. Hochberg and Lederer emphasized the fact that patients with carcinoma of the lung may have no symptoms referable to the chest at the time of admission. Of 47 patients who had thoracic symptoms, cough was present in 91.5 per cent. In the 13 cases in which there were no thoracic symptoms, the most frequent complaints were as follows: epigastric distress in 7 (53.9 per cent); anorexia in 7 (53.9 per cent); nausea and vomiting in 6 (46.2 per cent); malaise in 5 (38.5 per cent); loss of weight in 4 (30.8 per cent); constipation in 4 (30.8 per cent), and aphasia in 2 (15.4 per cent). These authors found that when the lesion involves the lower lobe of the left lung the epigastric distress is most likely to be a disturbing factor. At first the cough is

usually nonproductive, but later it is accompanied with expectoration. Although early, the expectoration may be scanty and mucoid; later it becomes more profuse and mucopurulent. It is frequently blood tinged and in the late stages may be foul.

Not infrequently the patient's attention is directed toward the thoracic involvement by evidences of an acute infection of the respiratory tract, such as acute bronchitis or influenza. Many of the patients are treated for a time for this infection, without improvement. Hemoptysis is a relatively infrequent manifestation, but when it does occur it is of great significance. In 1 of our patients the only symptom was hemoptysis of two weeks' duration. In 25.8 per cent of Brines and Kenning's series, symptoms of an acute infection of the respiratory tract were the initial manifestation. In their series, hemoptysis was the chief complaint in 18.9 per cent but was present at some time during the course of the illness in 48.3 per cent. Simons reported its presence in 40 per cent of his collected series.

Relatively frequently an indefinite pain is felt in the thorax, which is likely to be disregarded by the patient. It was present in 60 per cent and was the chief complaint in 44.8 per cent of Brines and Kenning's series. These respective incidences were 71.7 per cent and 21.7 per cent in Frissell and Knox's series; Simons found it present in 59.8 per cent of his collected series. Polevski expressed the opinion that pain is the most frequent complaint. Fried emphasized the persistence of the pain in spite of therapy. Pain may be the earliest symptom of the more peripherally located lesions.

Dyspnea occurred in almost 60 per cent of both Simon's and Frissell and Knox's series. However, since autopsy cases are the bases for these incidences, dyspnea cannot be regarded as an early symptom. Obviously, dyspnea cannot be considered an early manifestation, because in order to produce this symptom the lesion must have sufficient time to interfere with function either by its size or by pleural effusion.

Unfortunately, a patient with early carcinoma of the lung has no symptoms which are characteristic of the condition, and any respiratory manifestations in a patient past 40 years of age should be investigated in order to exclude the possibility of a pulmonary malignant tumor. This statement is sufficiently justified by the high incidence of carcinoma of the lung. Only by such constant vigilance can the early diagnosis of carcinoma of the lung be made. An acute infection of the respiratory tract which does not subside within a reasonable time in a patient past 40 years of age should be considered as due to a primary malignant tumor of the lung until this has been definitely excluded. In cases of peripherally located tumors with extension to the pleura, evidences of pleurisy with effusion may be present. Symptoms which appear late are loss of weight and strength, cyanosis, dyspnea and hypertrophic

pulmonary osteoarthropathy. Owing to circumferential growth, the vascularity of the tumor in its central portion becomes impaired, which results in necrosis and abscess formation. Pulmonary abscess without antecedent pneumonitis or aspiration of a foreign body should be considered of malignant origin until proved otherwise.

The duration of symptoms in the reported series varies considerably, but generally the interval from the first onset of symptoms until death is relatively short. Koletsky stated that the average duration of symptoms from onset until death is about six months. Brines and Kenning found that 4 per cent of patients had symptoms less than a month; 27.8 per cent, from one to three months; 39.7 per cent, from three to six months; 9.2 per cent, from six to nine months, and 7 per cent, for more than a year. King found an average duration of life of nine and three-tenths months. Frissell and Knox had 1 patient with symptoms of less than a month's duration; 15 with symptoms of less than three months' duration; 13 with symptoms of less than six months' duration; 9 with symptoms of less than twelve months' duration; 5 with symptoms of less than fifteen months' duration, and only 3 with symptoms lasting over fifteen months. The average length of life in D'Aunoy, Pearson and Halpert's series of cases was five months. Their figures would indicate that carcinoma of the lung is a rapidly progressive condition. From our clinical experience we do not believe that this is the case; we are inclined to consider the statistics presented by these authors as not necessarily indicative of the true duration of symptoms. The histories were probably taken by persons who did not consider the possibility of carcinoma of the lung and consequently made no serious effort to elicit the inaugural symptoms. Moreover, it should be realized that in many instances the condition is undoubtedly present for a long time before the onset of symptoms. In 1 of our cases a man who was a heavy smoker had no symptoms except a cough which had not changed in character over a period of years. Hemoptysis, which was the first manifestation, was noticed two weeks before his admission to the hospital. The roentgenograms showed a relatively large tumor, involving the hilar region, which was found inoperable on subsequent exploration. Two other patients with chronic cough, which was thought to be due to cigaret smoking, had relatively acute manifestations of only a few weeks' duration and were found to have large neoplasms following pneumonectomy. Another patient, a year prior to his first manifestation, had had a roentgenogram taken as part of a routine examination. At that time the roentgenogram was thought to be normal, although there was a slight hilar enlargement on the left side. One year later he had an acute infection of the respiratory tract, which was diagnosed as influenza. A roentgenogram taken at this time showed the same hilar enlargement

and the diagnosis of bronchogenic carcinoma was not suspected until several months later, when atelectasis of the lung distal to the involved bronchus developed.

The physical findings in cases of pulmonary malignant tumor are as protean as the symptoms and are dependent on the location and extent of the lesion and the consequent secondary pulmonary changes. We have frequently observed no physical changes in cases in which the diagnosis was made by roentgen and bronchoscopic evidence. Limitation of expansion, dulness, decreased breath sounds and rales occur with great variability and are most frequently present in the late stages. In fact, the presence of obvious physical signs is generally indicative of inoperability.

#### DIAGNOSIS

The most important factor in the diagnosis of pulmonary carcinoma is the consideration of its possible presence. It should be suspected in the case of every patient 40 years of age or older with cough, hemoptysis or thoracic discomfort. Undoubtedly, in the past many, if not most, pulmonary carcinomas have been incorrectly diagnosed. Thus, Sehr, in 1904, reported only 3.3 per cent of correct antemortem diagnoses in a series of 178 cases. This incidence of correct diagnoses was 36.8 per cent in Probst's cases, 30 per cent in Kikuth's and 20 per cent in those of Cottin and his co-workers. Koletsky found that a correct diagnosis was made in only 56 per cent of his cases. In 9 cases a diagnosis of tuberculosis was made. In an additional 9 cases a diagnosis of abscess was erroneously made. Undoubtedly, the high incidence of incorrect diagnoses is due in great part to the ability of cancer of the lung to simulate other conditions. However, of even greater importance in this regard is the frequent lack of its consideration.

Whereas roentgenographic examination without the use of contrast mediums is usually of little or no value in the *early* diagnosis of non-obstructive bronchial neoplasms, careful stereoroentgenographic studies are necessary for all such lesions. The roentgen interpretation of centrally located lesions is generally more difficult because of the confusion with hilar shadows produced by other lesions and by normal structures. This is particularly significant because most pulmonary neoplasms occur in the hilar region. This is emphasized by the case mentioned, in which a roentgenogram taken a year before the onset of symptoms, in which a hilar shadow was demonstrated, was considered to be of no consequence. With centrally located lesions, after the condition has progressed to such an extent that bronchial obstruction occurs, atelectasis of one or more lobes develops, depending on the degree of central location. The physical and particularly the roentgen manifestations of carcinoma of the lung are characteristic, that is, dulness or shadow and displacement of the medias-

shadow. Roentgenograms taken after the intratracheal or intrabronchial injection of iodized poppyseed oil may demonstrate partial or complete occlusion of the bronchi. The oil may be instilled by numerous technics. However, one of the simplest is the transglottic method previously described.

The presence of malignant cells in expectorated material can frequently be demonstrated microscopically. By this method of examination Dudgeon found carcinoma cells in 60 per cent of patients in whose cases a diagnosis of pulmonary neoplasm subsequently was proved. This method of diagnosis has been successfully used more recently by Barrett and by Gamba and Lamberti. In using this method it is important, as was emphasized by Edwards, that the pathologist examining the tissue be particularly trained in the recognition of these cells. Similarly, the demonstration, according to Mandlebaum's technic, of malignant cells in the pleural fluid in those cases in which there has been extension to the pleura is of diagnostic importance. Seecof demonstrated malignant cells in about 70 per cent of cases and Goldman in about 80 per cent. This method is of little use early in the disease, however, because of the relatively late extension to the periphery except in peripherally located lesions. The importance of this method of diagnosis lies principally in its prognostic value.

Aspiration biopsy has also been suggested as a diagnostic method.<sup>27</sup> Whereas we previously advocated and practiced aspiration biopsy, we feel that this procedure should be condemned because of the danger of metastases occurring in the pleura as a result of the removal of the specimen. That this is not only a possibility but a probability is evidenced by a case reported by Dolley and Jones, in which a metastatic nodule developed in the thoracic wall after aspiration of pleural fluid.

#### TREATMENT

Although there is considerable controversy among surgeons and radiologists concerning the relative values of surgical extirpation and irradiation for malignant tumors elsewhere in the body, at present it is the consensus that the only curative treatment of carcinoma of the lung is surgical extirpation. This is particularly true because of the almost hopeless outlook following the use of other types of therapy. Irradiation, either external or internal (by means of implantation of radon), has been used as a palliative procedure and is of value in hopeless cases in alleviating the manifestations.<sup>28</sup> In a series of patients treated by irradiation

27. Craver and Binkley; Martin and Ellis; Sharp.

28. Baum; Butler and Ritvo; Harper; Konrad and Franke; Leddy and Vinson; Manges; Meland; Paterson; Pressman and Emery; Roberts; Stern; Tyler; Vinson; Vinson and others; Wood and others.

tion, King found that the average duration of life for those treated was fifteen and four tenths months as compared with nine and three tenths months for the entire series of cases. Chandler and Potter found that the average duration of life for 59 patients treated by irradiation was eleven months, whereas that for 61 untreated patients was six months. Ormerod also observed a slight increase in the duration of life of the treated patients. Brock, in a series of 106 cases, advised local radon therapy in 10. In all but 3 of these the radon therapy was suggested merely as a placebo. He stated the opinion that irradiation has little to do with prolonging life and that in those cases in which the patient's life is apparently prolonged it is probably because the carcinoma grows slowly. He referred to a patient who lived eight years after his first symptoms without any treatment. Saupe similarly found that only about 15 per cent of 200 patients showed definite improvement following irradiation. Numerous others<sup>29</sup> have also observed that irradiation for carcinoma of the lung is of little if any value.

Although in a number of reported cases<sup>30</sup> simple resection of the involved lobe has been performed, it seems to us that any procedure short of total removal of the involved lung is irrational. Only by complete excision of the entire lung can the primary focus be adequately removed. Moreover, lobectomy obviously does not permit removal of the regional lymph nodes. As has been mentioned, the fact that the incidence of lymph node involvement is relatively high is sufficient indication that the regional lymph nodes should be extirpated together with the primary lesion. The performance of simple lobectomy for carcinoma of the lung is just as illogical as is partial removal of the breast with no attempted extirpation of the regional lymph nodes for mammary carcinoma. Another reason for total pneumonectomy is that approximately 75 per cent of pulmonary neoplasms originate in the proximal bronchi. As was shown by Bonniot, Monod and Evrard, it is not possible to apply a tourniquet high enough on the pedicle of the lung to permit division of the main bronchus without injuring the pericardium or other mediastinal structures. Although total pneumonectomy may seem a radical procedure, particularly for an elderly patient suffering from a pulmonary neoplasm, it should be realized that in operations for malignant tumor complete extirpation is a requisite for cure. Moreover, from a technical standpoint, total pneumonectomy is a much better procedure, surgically and anatomically, than is lobectomy. The latter at best is more or less a

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29. Bonner; Fried; Frissell and Knox; Hunt; Kaplan; Kernan; Maxwell and Nicholson; Pancoast and Pendergrass; Robet; Rodenbaugh; Rubenstone and Schwartz; Seifert; Simpson; Stachelin; Tuttle and Womack.

30. Dolley and Jones; Graham and others.

makeshift operation. It is almost invariably necessary to cut through pulmonary tissue because of the incomplete division of the lung by the fissures.

As a preliminary procedure, artificial pneumothorax should be performed over a period of time. This is done in stages, the amount of intrapleural pressure being increased gradually until the pressure is definitely on the positive side. Preoperative pneumothorax is of diagnostic importance in determining the presence, the extent and the location of adhesions, thus permitting the preoperative planning of the operative procedure. It is desirable also in determining the extent of the adhesions to take roentgenograms with the patient's head down, in order to determine the extent of adhesions between the base of the lung and the diaphragm. Another decided advantage of preoperative pneumothorax is the gradual compression of the pulmonary capillary bed, which gives the heart time to compensate for the increased peripheral resistance in this area and thus mitigates the sudden change which follows the cutting off of the blood to the involved lung at the time of ligation of the pulmonary vessels. This is particularly true with elderly persons whose cardiac reserve is diminished and in whom malignant tumors of the lung are likely to occur. Whereas previously we believed that it was possible to bring about the collapse within a relatively short period, i. e., a few days, at present we are of the opinion that the period of compression should be more prolonged and that at least ten days to two weeks is required for complete compensation of the cardiovascular system before operation. We have not used the preoperative instillation of beef broth bouillon into the pleural cavity as suggested by Rienhoff.

Preoperative administration of unmodified blood is usually of importance. When the patient has anemia, it is imperative that at least two donors be available at the time of operation. Although we have had one massive hemorrhage occur during the course of an operation, this was early in our experience, and subsequently it has seldom been necessary to give a transfusion postoperatively, because of the minimal amount of blood lost.

*Anesthesia.*—Although pneumonectomy may be performed with local or spinal analgesia, the latter being particularly popular in Canada and England, we prefer cyclopropane inhalation anesthesia. Because of the wide opening in the chest wall, it is necessary that the anesthetic be administered under positive pressure. In our earlier cases intratracheal tubes were used, but we are convinced that the use of intratracheal tubes is deleterious, because of the likelihood of the introduction of infection and the increased secretion resulting from trauma, which in the presence of a single lung after pneumonectomy is particularly dangerous. One of our fatalities, previously reported, which occurred fourteen hours after operation, undoubtedly was due to trauma of the trachea by the

intratracheal tube resulting in such excessive secretion that the patient virtually drowned in her own secretion despite almost continuous aspiration.

Although we have used both the posterior approach of Crafoord and the anterior approach of Rienhoff to satisfaction and although in our previous publication we expressed the opinion that for basal lesions the posterior approach is preferable, we believe that with few exceptions the anterior approach is not only adequate but preferable. It has the distinct advantages that a relatively shorter incision is used and the opposite, uninvolved lung is not compressed (by the position of the patient on the operating table) during the operative procedure. In contrast to the intercostal incision as suggested by Rienhoff, we prefer subperiosteal resection of the third rib and its adjoining costal cartilage. The incision is made along the course of the third rib, extending from the midportion of the sternum to the midaxillary line. The fibers of the pectoralis muscles are separated in the direction of the incision. In separating the perichondrium from the third costal cartilage, care should be taken to avoid injury to the internal mammary vessels. After removal of the third costal cartilage and the anterior portion of the third rib, the remaining portion of the costal cartilage is removed from the sternum by means of rongeurs. The internal mammary vessels are then secured both above and below the line of incision by means of a transfixion suture of no. 2 silk. Prior to the use of this procedure, troublesome and occasionally alarming hemorrhage occurred from these vessels. It is necessary that the vessels be divided in order that an adequate approach to the mediastinum can be obtained. The pleura is opened through the bed of the third rib throughout the extent of the incision extending from the lateral border of the sternum to the anterior axillary line.

After the pleural cavity has been opened the lung is mobilized by division of adhesions by sharp dissection. In the anterior approach the lung is retracted posteriorly in order to expose the lateral surface of the mediastinal pleura. An incision is made in the mediastinal pleura, in the groove of the reflection of the pleura from the mediastinum to the medial surface of the lung. A flap of mediastinal pleura is thus formed, which is elevated to expose the mediastinal and hilar structures. This is greatly facilitated by the use of long, ball-tipped, slightly curved scissors. Care is taken in mobilizing this flap to avoid injury to the phrenic nerve and the pericardiophrenic vessel. After its exposure the phrenic nerve is crushed by means of artery forceps in order to paralyze the homolateral side of the diaphragm for a period of months.

The mediastinal structures are isolated individually. Mass ligation of the hilus is to be condemned as an unsurgical procedure and one which will give bad results in the majority of cases because of incomplete extirpation. It does not permit removal of the mediastinal lymph nodes



in which metastases are likely to occur and in many instances does not permit the complete removal of the tumor. On the right side, in addition to isolation, quadruple ligation and division of the pulmonary artery, the two pulmonary veins and the bronchus, the azygos vein should be ligated and divided. This is necessary because of the difficulty of freeing the bronchus if such a procedure is not used. In 1 of our cases, because of incomplete ligation of the azygos vein there was slipping of the ligature, which resulted in fatal hemorrhage. This case has been reported previously. The individual isolation of the hilar structures, beginning with the pulmonary artery, is imperative. This artery is isolated from the remaining structures principally by blunt dissection, with small gauze pledgets and the curved Semb dissector. After the pulmonary artery has been isolated for a distance of approximately 1.5 to 2 cm., a no. 2 silk ligature is passed around the vessel and tied as far proximal as possible. A similar ligature is placed around the distal side and tied. Proximal and distal to these ligatures are inserted transfixion sutures, which are tied on both sides of the vessel. Thus the vessel is quadruply ligated, a transfixion and a plain suture being placed medially and a plain and a transfixion suture distally. The vessel is divided between the ligatures, care being taken to leave sufficient length of vessels on the medial aspect. The superior pulmonary vein is similarly treated, after which the bronchus is isolated and crushed by means of two large forceps and divided between these with a scalpel. Interrupted mattress sutures are placed proximal to the forceps, after which the forceps are removed; the crushed end of the bronchus is then closed with interrupted silk sutures. Finally, the inferior pulmonary vein is treated as described for the pulmonary artery and superior pulmonary vein. All of the mediastinal lymph nodes on the affected side are extirpated in order to remove any possible metastatic foci. After complete extirpation of all mediastinal lymph nodes, careful pleuralization of the mediastinum is imperative. Whenever possible, the edges of the divided mediastinal pleura are approximated, and the stumps of the ligated vessels and bronchus are covered with pleura. If there is an insufficient amount of pleura to cover the hilar stump satisfactorily, a pleural flap from the pericardium or from the lower part of the mediastinal pleura is swung into position to cover the bronchial stump as suggested by Rienhoff. This is important in order to minimize the danger of infection and to augment prompt healing of the bronchial stump. In our cases we have not resorted to drainage, because we believe with Rienhoff that filling of the pleural cavity with fibrinous exudate is important in obliteration of the cavity. Obliteration of the cavity also is facilitated by elevation of the diaphragm, which follows crushing of the phrenic nerve at the beginning of the operation. The thoracic wound is closed tightly, interrupted no. 1 silk sutures being used for the pleura and the intercostal muscles. The

superficial muscles and the skin are closely approximated by means of the same material. A compression sea sponge bandage is applied over the wound to obliterate the dead space and to lend support to the wound.

In a previous report we analyzed 79 reported cases of total pneumonectomy for neoplastic disease of the lung. In addition to this number, we reported 7 pneumonectomies which we had done, making a total of 86 cases. In this presentation, the number of total pneumonectomies for neoplastic disease of the lung, including those done by us, will be brought up to date. There have been 22 additional pneumonectomies reported, and we have performed 8 additional ones, making a total of 101 reported pneumonectomies<sup>18</sup> and 15 of our own, a grand total of 116 total pneumonectomies for neoplastic disease. In 94 of the collected cases in which a statement was made concerning the outcome, 38 patients recovered and 56 (59.5 per cent) died. Of 15 of our patients, 7 recovered and 8 (53.3 per cent) died (fig. 10). In the total of 109 cases, including the collected series and our own cases, 45 patients recovered and 64 (58.7 per cent) died. In 52 of the collected cases in which the sex was stated, there were 38 male and 14 female patients. Of our 15 patients, 12 were males and 3 females. In the entire group of cases there were 50 (74.6 per cent) male patients and 17 (25.3 per cent) female patients. The age incidence for the collected cases and our own cases in which a total pneumonectomy was done was as follows: from 0 to 9 years, 2 (2.9 per cent); from 10 to 19 years, 2 (2.9 per cent); from 20 to 29 years, 2 (2.9 per cent); from 30 to 39 years, 8 (11.9 per cent); from 40 to 49 years, 25 (37.3 per cent); from 50 to 59 years, 24 (35.8 per cent), and from 60 to 69 years, 4 (5.9 per cent). Of 70 cases in which the site involved was stated, the left side was involved in 37 (52.8 per cent) and the right in 33 (47.1 per cent). Of 53 cases in which the involved lobe was stated, the upper lobe of the right lung was involved in 9 (16.9 per cent); the upper lobe of the left lung, in 14 (26.2 per cent); the lower lobe of the right lung, in 15 (28.3 per cent); the lower lobe of the left lung in 10 (18.8 per cent), and the middle lobe of the right lung in 5 (9.4 per cent). Of the 33 patients with lesions on the right side, 12 recovered and 21 died (63.6 per cent). Of the 37 with lesions on the left side, 17 recovered and 20 died (54 per cent). This is of importance because, as we have emphasized in previous publications, it is our opinion that a pneumonectomy on the left side is relatively easier than one on the right side because of the presence of the azygos vein in the latter instance. In 24 cases in which massive ligation was done, 5 patients recovered from the operation (20.8 per cent), and 19 died (79.1 per cent). One of these patients, however, subsequently died of metastases, and it is fair to assume that if massive ligation had not been done, this death might have been pre-

vented, leaving 4 who recovered (16.6 per cent) and 20 (83.3 per cent) who died after massive ligation. In 54 cases of total pneumonectomy for pulmonary neoplasm in which individual ligation of the hilar structures was done, 25 patients (46.2 per cent) recovered and 29 (53.7 per cent) died. This illustrates the advisability of using individual ligation not only because a much more radical procedure can be done but because the mortality rate is definitely lower. Of the 45 patients who recovered, 8 have subsequently died (6.8 per cent of the entire group). These were reported as follows: by Archibald, 1; by Churchill, 2; by Crafoord, 1; by Overholt, 3, and by us, 1. In 104 cases in which the type of neoplasm was stated, there were 97 (93.2 per cent) carcinomas, 2 (1.9 per cent) metastatic melanomas, 1 (0.9 per cent) metastatic sarcoma and 4 (3.8 per cent) primary sarcomas. Of the 51 cases in which the cause of death was stated, there were 20 (39.2 per cent) in which it resulted from infection and pneumonia; 12 (23.5 per cent) in which it was due to cardiac failure and pulmonary edema; 7 (13.7 per cent) in which it was due to hemorrhage; 5 (9.8 per cent) in which it was caused by metastases; 4 (7.8 per cent) in which thrombosis and embolism were the cause, and 1 each (1.9 per cent) in which it was due to shock, peritonitis and asphyxia.

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# OBSTRUCTION FOLLOWING GASTROENTEROSTOMY OR SUBTOTAL RESECTION OF THE STOMACH

TREATMENT BY JEJUNOPLASTY

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Obstruction is a major and grave complication of gastric surgical procedures. Always serious and frequently calamitous, it ranks in importance second only to marginal ulcer and its sequelae. It is difficult to state with what frequency this complication occurs, for in contrast to the early days of surgery, the complication is today passed off as occasional, and few surgeons have recorded and published their figures. That the incidence is more than "occasional" is evidenced by the continuous shift in choice of procedures from one type of operation to another in an endeavor to avoid the grave consequences of its occurrence. Indeed, many surgeons at the moment have reverted to unions of the antecolic type,<sup>1</sup> and there is an increasing tendency toward more radical measures, with resection of more or less of the stomach with or without entero-anastomosis. However, all surgeons are compelled at times to resort to gastroenterostomy of either the antecolic or the postcolic type when more radical surgical treatment is not feasible. Regardless of the method employed, even in the hands of the most skilled surgeons<sup>2</sup> occasional cases of obstruction are met with, and one may well ask how frequently this occurs with the less gifted or the occasional operator. As knowledge of the frequency of this complication is unsatisfactory, so too is knowledge of its mortality. We would hazard a guess, in view of the apparent lack of uniformity of treatment throughout the United States, that it is perhaps comparable in percentage to that of acute appendicitis.

Obstruction is probably more common after gastroenterostomy than after some of the more radical procedures. In those operations in which

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1. Marshall, S. F., and Kiefer, E. D.: Partial Gastrectomy for Gastric or Duodenal Ulcer, *J. A. M. A.* **109**:1341 (Oct. 23) 1937.

2. Graham, R. R.: *Surg., Gynec. & Obst.* **66**:269, 1938.



the end of the stomach is anastomosed directly to the jejunum, the stoma tends to open when the stump of the stomach is distended and can accommodate itself more readily to the available space than in the case of a gastroenterostomy. In the discussion that follows, gastroenterostomy is used as a type operation, not because we think it a preferable means of treating lesions of the upper alimentary tract but because all of the causes of obstruction may be associated with it.

#### CAUSES OF OBSTRUCTION

Obstruction after gastroenterostomy may occur from one or more of the following causes:

*An Improperly Placed Stoma.*—Although there have been differences of opinion among surgeons as to the exact line of the anastomosis in a gastroenterostomy, we agree with Eusterman and Balfour<sup>3</sup> that the position of choice is at the most dependent part of the stomach and that the long axis of the stoma should lie nearly at right angles to that of the stomach (fig. 1 A). On completion of the operation the distal portion of the jejunum should be in contact with the greater curvature and should point toward the left hip. Unless care is exercised, malposition may occur, especially if gastric dilatation is present, for this makes it difficult to ascertain which portion of the stomach will be more dependent when the upright posture is assumed. Furthermore, as the approach is so often in the midline and as the greater part of the stomach lies to the left, it is not uncommon for the surgeon to find that his anastomosis lies much nearer to the pylorus than he had anticipated.

*A Stoma Too Small in Itself or So Narrow of Attachment as to Produce Acute Angulation of the Jejunum.*—The stoma may have been initially made too small or rendered so either because the stomach was dilated at the time of operation and later contracted or because an unusual amount of the tissue was inverted during suture of the anastomosis. When the stoma is wide, a longer segment of intestine is in actual contact with the stomach; the limits of the attached loop are more widely separated, and the angulation is more obtuse. There is therefore less likelihood that one loop will become distended and compress the other or that kinking or rotation will occur.

The uniformly excellent function following subtotal gastric resection when the entire end of the stomach forms an extremely large stoma has resulted in less emphasis being placed on the question of too sudden emptying of the stomach. It is the small, not the large, stoma which gives trouble.

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3. Eusterman, G., and Balfour, D. C.: *The Stomach and Duodenum*, Philadelphia, W. B. Saunders Company, 1935, pp. 305, 308 and 310.

*A Proximal Loop of Excessive Length or of Such Shortness as to Obstruct with Changing Position of the Stomach.*—The establishment of the so-called vicious circle through the overfilling of an unduly long proximal loop and the production of intermittent obstruction is now well known. An excessively short loop may produce much the same symptoms.<sup>3</sup> A stomach empty and contracted may lie high in the epigastrium at operation. When filled it may sag toward the pelvis, and if the proximal loop is too short to accommodate the changing position of the stomach the anastomosis, dragged on, may be twisted, kinked and obstructed.

*A Rigid and Short Mesocolon Which Fails to Stretch on Filling of the Stomach.*—The importance of the transverse mesocolon in the success or failure of a gastroenterostomy is still not fully appreciated by many surgeons. As a rule the mesocolon is thin and pliable and accommodates itself to the changing positions of the stomach. On occasion it is naturally thick and resistant or has become rigid from fatty deposit or inflammation. If trouble is to be avoided under these circumstances the opening in the mesocolon must be made unusually large and the stomach drawn well through and firmly sutured in this position. Otherwise, as the stomach fills and its walls straighten out the anastomosis may be pulled up and become obstructed. The rigid, short mesocolon is, in the opinion of Balfour, unsuitable for posterior gastroenterostomy.

*Inadequate Fixation of the Stomach to the Mesocolon and Internal Hernia.*—Obstruction from herniation of a part of the anastomosis or of a distal loop of intestine into the lesser sac when the fixation of the mesocolon to the stomach is inadequate has long been recognized.

*Adhesions About the Stoma.*—Adhesions in the region of the stoma due to peritoneal soiling, leakage or trauma may cause cicatrization resulting in obstruction, which becomes manifest late in the period of convalescence.

*Pressure of the Middle Colic Artery.*—McCaughan and Coughlin,<sup>4</sup> in reporting a case, pointed out that if the opening in the mesocolon is made to the right of the middle colic artery this vessel may produce obstruction by pressure on the two limbs of the anastomosed jejunum.

*Marginal or Jejunal Ulcers At or Near the Stoma.*—The edema accompanying gastrojejunal or jejunal ulcers and the contraction which follows may produce partial or complete obstruction. Experimentally we have observed in the dog after gastroenterostomy the presence of ulcers on and about the stoma only in those cases in which a continuous nonabsorbable suture had been employed, findings similar to those reported by Wilkie<sup>5</sup> many years ago.

4. McCaughan, J. M., and Coughlin, W. T.: Surg., Gynec. & Obst. 65:824, 1937.

5. Wilkie, D. P. D.: Edinburgh M. J. 5:316, 1910.

*Adhesions Distal to the Anastomosis.*—Adhesions about the abdominal closure or elsewhere may give rise to all signs and symptoms of obstruction at the stoma. However, the onset of symptoms is usually delayed.

*Hypoproteinemia.*—Recently Ravdin and Rhoads<sup>6</sup> have shown both clinically and experimentally that a protein deficiency may be responsible for edema and a lack of motility which produce obstruction. This, for the first time, offers a logical explanation for some of those cases in which at operation no mechanical difficulty has been found.

*Comment.*—In anterior gastroenterostomy the mesocolon is eliminated as an element of trouble only to have the long loop of jejunum required for the anastomosis substituted for it, and, although an enteroanastomosis may prevent obstruction, it has the disadvantage of removing the neutralizing action of the alkaline duodenal contents.

It should be noted that all the factors enumerated as causes of obstruction are, with the exception of distal adhesions, operative in the immediate vicinity of the anastomosis itself. Patients in whom obstruction develops can be divided into four groups: (1) those who have gastric retention immediately after operation but who are eventually relieved by conservative treatment, which shows that the obstruction was due to edema and swelling; (2) those who still have obstruction after seven to fourteen days of conservative treatment, which indicates that the obstruction is mechanical; (3) those who have been able to take food satisfactorily during the early part of the postoperative period and subsequently show signs of obstruction (in such patients the obstruction is usually due to adhesions but occasionally may be adynamic), and (4) those who show, weeks or years after operation, either complete or incomplete obstruction caused by a marginal ulcer or its complications.

Patients in groups 2 and 3, in which obstruction occurs late, present a problem of the greatest urgency. Often no exact diagnosis of the cause of the obstruction is possible. Roentgen examination is not helpful for, apart from the fact that the stomach fails to empty, no reason for the obstruction is obvious, in that the barium sulfate mixture fails to pass the stoma. Too frequently the abdomen is opened and, after considerable dissection, the stoma is exposed and found on palpation to be open and apparently satisfactory. The gravity of the patient's condition compels the perplexed surgeon reluctantly to perform an enteroanastomosis or a jejunostomy, hurriedly closing the abdomen. The failure to make a diagnosis is due to the fact that at no time was it possible to observe the bowel during peristaltic effort. Of those patients heretofore subjected to operation it is not improbable, considering all cases, that 75 per cent

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6. Ravdin, I. S., and Rhoads, J. E.: S. Clin. North America 15:85, 1935.  
Ravdin, I. S.: Surgery, 1:53, 1937.

have failed to survive, owing to the fact that either nothing has been accomplished or operation has been delayed too long. We believe that the following program should be carried out in the early stages of every obstruction and that if the patient fails to respond operation should be done immediately.

#### TREATMENT

*Conservative Therapy.*—Conservative measures consist of (1) gastric lavage (by the Robertson Ward method as popularized by Wangensteen or by use of the Miller-Abbott or the Abbott-Rawson tube); (2) careful calculation of the water balance, with maximum dextrose and limited salt; (3) administration of protein in the form of whole blood or blood serum (250 cc. or more daily) to combat hypoproteinemia; and (4) feedings of thick gruel after the stomach has contracted and the dextrose, protein, salt and water balance is corrected. If these measures fail to give relief in seven to fourteen days for patients of group 2 (even earlier for those of group 3), the time depending on the patient's general condition, we believe that reoperation should be done without delay.

*Operative Therapy.*—The following procedures may be considered: 1. The breaking up of adhesions which may be found distal to the anastomosis quickly relieves the obstruction. The release of adhesions near the stoma, however, frequently fails to give permanent relief. 2. Enteroanastomosis below the stoma has proved disappointing as an emergency measure and besides provides conditions favorable to the development of a marginal ulcer. 3. Jejunostomy may be equally unsatisfactory, because there is no assurance that it will give relief, and it frequently superimposes a local obstruction or infection on an already serious condition. Moreover, in the light of the work of Ravdin and Rhoads<sup>6</sup> it seems reasonably certain that patients who heretofore have been eventually relieved by this long and uncertain procedure can be cured within four or five days by the administration of protein. 4. Restoration by taking down the anastomosis and the more radical resections are procedures which few patients can be expected to survive. 5. Jejunoplasty, the operation recommended in this paper, may be done.

#### JEJUNOPLASTY

A year ago<sup>7</sup> we proposed an operative procedure designed to relieve obstruction at the level of the stoma. It requires a minimal amount of operative handling and has given such effective and prompt relief that we believe it to be the operation of choice.

1. *Technic of Jejunoplasty for the Relief of Acute Obstruction.*—A jejunoplasty is virtually the application of the principles of the Finney pyloroplasty to the two limbs of the jejunum at the site of the anastomosis.

7. Hoag, C. L., and Saunders, J. B. de C. M.: Surg., Gynec. & Obst. 68:703, 1939.

When the abdomen has been opened and the possibility of obstruction from more distally placed adhesions has been excluded, the anastomosis is identified and brought into view. After the viscera have been carefully packed off, the proximal and distal limbs of the jejunum are placed side by side and their serosal surfaces sutured together for 2 to 4 cm. (fig. 1 *B*). An inverted U-shaped incision opening into both limbs of the jejunum is carried around the suture line just below the stoma (fig. 1 *B*). The stoma is then under direct inspection (fig. 1 *C*). When it has been determined that the stoma is adequate and that no ulcer or faulty mechanics exist, the opening in the jejunum is closed as in the Finney pyloroplasty<sup>8</sup> or one of its modifications<sup>9</sup> (figs. 1 *C*, 1 *D* and 2).

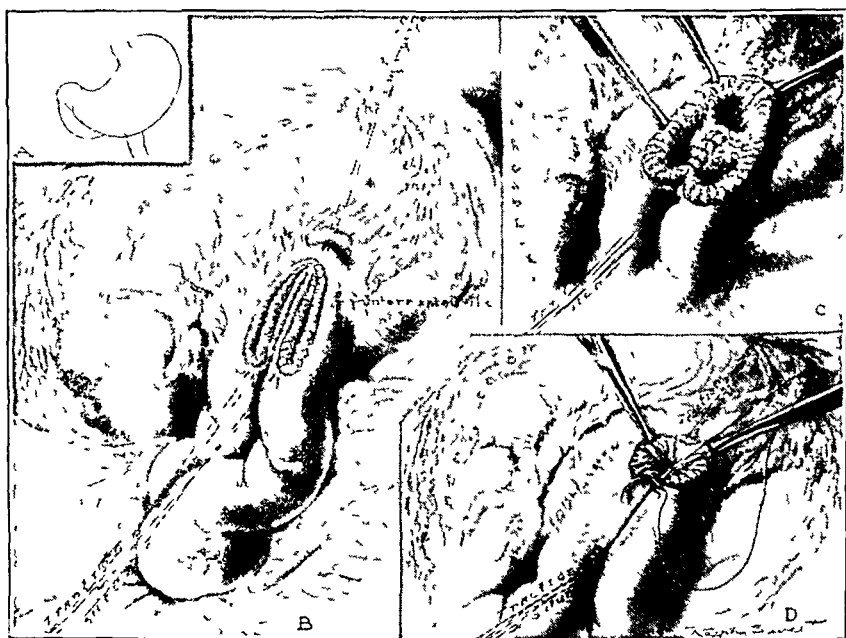


Fig. 1.—*A*, stomach and posterior gastrojejunostomy. *B*, a center point is selected and the jejunum on either side of the anastomosis is drawn parallel and united by interrupted silk sutures—the outer suture line. A horseshoe-shaped incision follows the lumen of the intestine and encircles the suture line. *C*, outer edge of the incision retracted, showing the stoma. Note the inner catgut interlocking suture line completing the posterior wall. *D*, inner catgut suture line carried to the anterior wall, completing the closure by use of the Connell stitch.

By this means a miniature secondary stomach, similar to that observed after gastroenterostomy or subtotal resection of old standing, is created. The septum between the two limbs is removed, and the double-barreled

8. Finney, J. M. T.: *Tr. Am. S. A.* **20**:165, 1902. Finney, J. M. T., and Hanrahan, E. C.: *Am. J. Surg.* **92**:620, 1930.

9. Finney, J. M. T.: *Surg., Gyn. & Obst.* **43**:508, 1926; *Surgery* **2**:748, 1937.

union becomes a single structure (fig. 3). In this way the stoma is freed of its dividing septum; the continuity of the jejunum is restored, and if any twist or compression of the jejunal loop existed it is corrected.

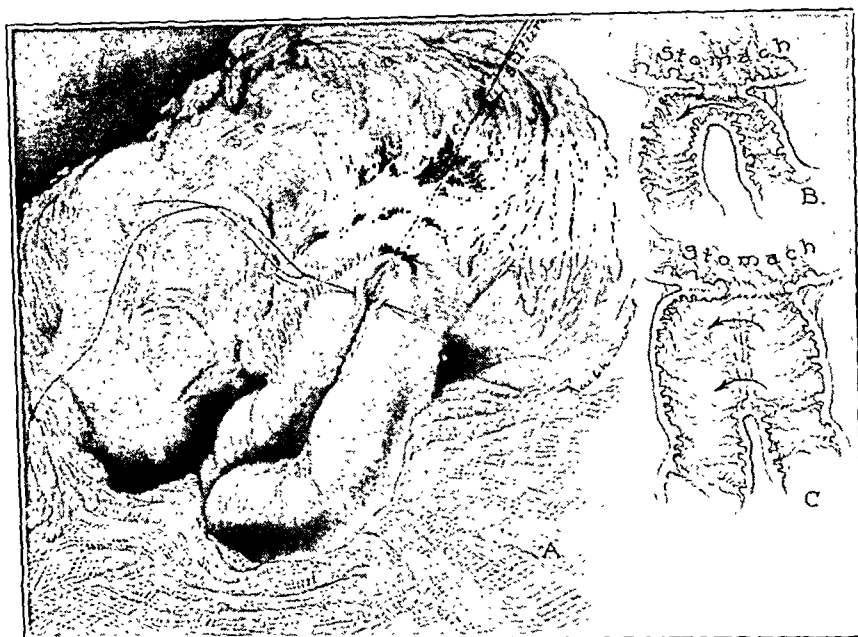


Fig. 2.—A, completion of the outer peritoneal suture line with interrupted silk sutures. B, sagittal section of the stomach, the stoma and the jejunum before jejunojejunostomy. C, picture after jejunojejunostomy.

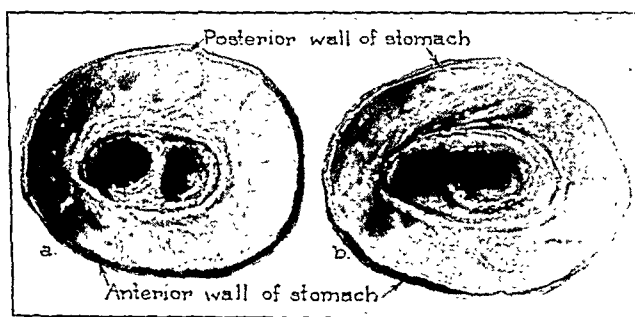


Fig. 3.—View of the anastomosis from within the stomach (a) before the jejunojejunostomy and (b) after the jejunojejunostomy, showing how the septum has been split down, restoring the continuity of the jejunal lumen and creating a potentially larger stoma.

2. *Correction of the Excessively Short or Long Proximal Loop.*—If the proximal loop of the anastomosis is found to be too short or too long, the error may be corrected to some extent by varying the relation

of the intestine (fig. 4). Maximal length in the proximal loop is gained by taking as center a point on the distal limb; maximal shortening, when this point is on the proximal portion of the jejunum and is used entirely for the jejunoplasty.

This procedure does not require the time or inflict the trauma incident to the breaking up of adhesions in an effort to expose the anastomosis.

3. *Variations of Technic in the Presence of Massive Adhesions.*—If it is not possible easily to identify both limbs of the anastomosis, the procedure can be modified as follows: The distal limb of the jejunum is

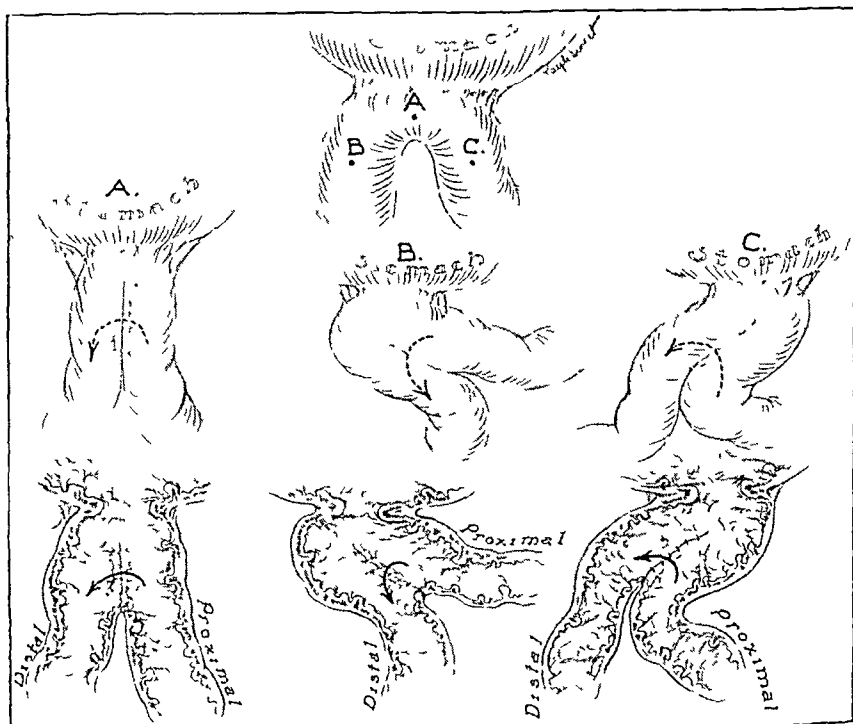


Fig. 4.—Sketch showing how the selection of a central point for starting the jejunoplasty will permit changing the length of the short loop and the resulting change in the lumen of the intestine. *A*, central point, with use of equal lengths of the proximal and distal part of the jejunum, shortened an equal amount. *B*, the length of the short loop is not changed by reflecting the distal part of the jejunum against it. *C*, maximum shortening of the proximal loop obtained by using this loop entirely for the jejunoplasty.

followed up to a point as near the anastomosis as is possible. A small longitudinal incision is made into the intestine, and a curved hemostat, a grooved lead probe or the little finger is introduced as a guide to determine the position of the anastomosis and the proximal intestine (fig. 5). The overlying adhesions are then divided and pushed back, and the intestine is opened over the guide, preferably by the use of



Fig. 5.—Operation in the presence of massive adhesions. A longitudinal incision is made in the distal part of the intestine as close to the gastroenterostomy as possible. A curved hemostat, a lead probe or the little finger is inserted to determine the direction of the intestine and the position of the stoma.

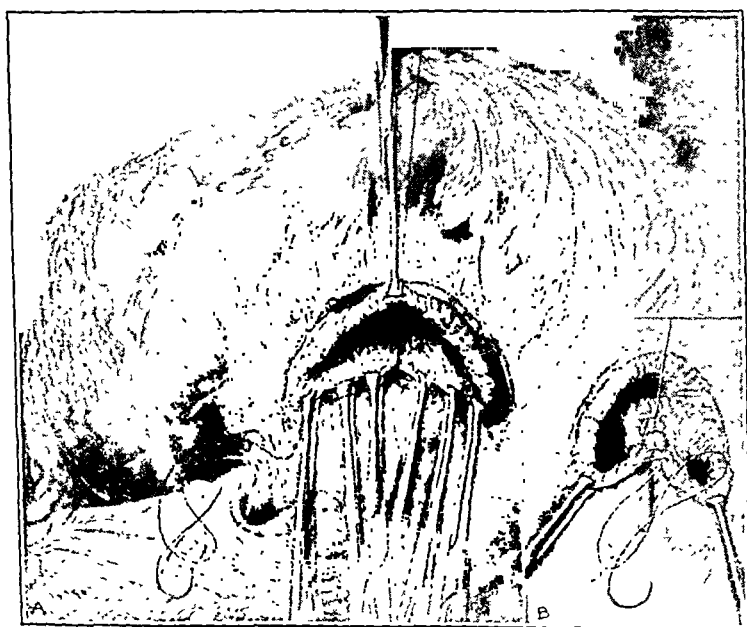


Fig. 6.—*A*, the intestine is split and the posterior edges are grasped with Allis forceps to control the profuse hemorrhage. A center is selected for starting the jejunoplasty, and the internal catgut suture is started and used as a tractor. *B*, the external row of sutures is placed and the internal catgut suture continued as in the uncomplicated case.



scissors curved on the edge. As the intestine is split, the posterior edge is grasped by a series of Allis forceps to control the hemorrhage, which is usually profuse. The stoma is then inspected; a center is selected for closure, and a double layer of sutures is then laid down as in the uncomplicated case (fig. 6).

#### ADVANTAGES OF THE OPERATION

This operation can be completed with no more shock and with as much dispatch as an ordinary enteroanastomosis. It possesses, as well, the obvious advantages of direct inspection of the stoma, together with correction at the site of obstruction. The procedure should be much more valuable than the usual jejunostomy or enteroanastomosis and should carry no greater operative risk.

The question may be asked as to the viability of the strip of jejunum lying between the incision and the original anastomosis. To determine the question of the circulation in this strip a large number of experimental operations were carried out on dogs. Occasionally there was a little cyanosis in this strip, but we found no necrosis or leakage in any instance *when the gastroenterostomy had existed for seven days or more*. Arterial injection in these animals indicated an adequate blood supply. However, as the strip is cut off from its primary blood supply, we recommend that the anterior suture line be routinely reenforced by the omentum as a precautionary measure. There is little danger of further obstruction from such reenforcement.

We do not believe that the jejunoplasty will increase the hazard of jejunal ulcer, for the procedure is designed simply to increase the lumen of the jejunum and to correct the faulty initial anastomosis. The possibility of marginal ulcer always exists with any gastrojejunal anastomosis. It would appear to be greater in that group of patients in whom there are sufficient mechanical defects to produce stasis or obstruction. Relief from these conditions should offset any hazard of ulcer incident to the operation itself. Moreover, it seems preferable to run that risk, if it exists, for the assurance of a living patient, even though the patient, like others with a gastrojejunal anastomosis, may eventually have marginal ulcer.

The relief afforded this group of patients with acute obstruction is striking and dramatic and is illustrated by cases to be reported.

#### REPORT OF CASES

CASE 1 (group 2).—H. W. S., a man aged 37 years, with a long history of duodenal ulcer, had been under medical treatment for two and one-half years. Owing to severe pain and persistent vomiting, together with a 20 per cent retention, operation was decided on after a preliminary period of rest in bed and daily gastric lavage.

Operation was performed on Sept. 17, 1930. The duodenum was found firmly fixed to the pancreas by a posterior ulcer. A short loop posterior gastroenterostomy was carried out, no difficulties being encountered. From the beginning of the postoperative period the patient was unable to take any great amount of fluid or food and continued to vomit except when his stomach was kept clear by Robertson Ward<sup>10</sup> suction. At the end of nine days a barium sulfate mixture did not pass, and it was evident that for some unknown reason the gastroenterostomy had failed to function.

Secondary operation was carried out ten days later (September 27). There were few adhesions: the distal loop was free; the stoma seemed adequate from without, and no kink or other cause of obstruction could be discerned. Every patient seen under like circumstances, including 2 of our own, had died, and in these cases no satisfactory explanation was rendered by autopsy. In pondering the question, the relation of the jejunal loops suggested to one of us (C. L. H.) the application of the principle of the Finney pyloroplasty for the relief of obstruction. When the jejunum was opened, the stoma, owing to contraction of the stomach, proved to be only one-half the size of that originally made. As no other abnormality was found, the operation was completed.

The patient was able to take fluids the next day and made an uneventful recovery. He had excellent relief from the original symptoms. He was not heard of again for two years, after which time he was operated on elsewhere for a ruptured appendix and died of general peritonitis. At autopsy a well functioning gastroenterostomy was demonstrated which could not be distinguished from that frequently seen long after the usual gastroenterostomy. The ulcer had healed.

CASE 2 (group 2).—C. H. L., 73 years of age, entered the hospital on Sept. 7, 1937, with a history of persistent vomiting and loss of weight. Roentgen examination showed an almost complete pyloric block, with a small niche on the lesser curvature, which was diagnosed as a probable carcinoma. Exploratory laparotomy on September 27 showed the stomach to be extensively infiltrated with carcinoma, which extended along the lesser curvature. No metastases were found. Because of the condition and age of the patient, a gastroenterostomy was done high on the posterior wall. He continued to vomit, and nothing passed through the gastroenterostomy opening.

On October 10 the abdomen was opened and a jejunoplasty was done as described. The patient's stomach began to empty immediately, and he made an excellent recovery. He was discharged on November 4.

CASE 3 (group 3).—J. E., 62 years of age, after medical treatment for a duodenal ulcer for a number of years, had suffered repeated severe hemorrhages which could not be controlled by a well conducted medical regimen. At operation, on Nov. 9, 1934, the stomach was found to be large and atonic, the pyloric end was densely adherent posteriorly and could not be freed. About 6 cm. beyond the pyloric vein there was a large indurated mass with much surrounding inflammatory reaction. It was deemed advisable to exclude this ulcer by performing a subtotal resection of the Mayo-Polya type. The duodenal end was closed, and a gastrojejunal anastomosis was done by the postcolic route. The mesocolon was short, thick and very heavy; it bled easily. The entire open end of the stomach

10. Ward, R.: Apparatus for Continuous Gastric or Duodenal Lavage, *J. A. M. A.* **84**:1114 (April 11) 1925; *California & West. Med.* **31**:395, 1929; *Am. J. Surg.* **8**:1194, 1930.

was anastomosed to the jejunum about 4 inches (10 cm.) from the ligament of Treitz. The mesocolon was carefully sutured to the stomach. The operation was completed without difficulty, and convalescence was excellent.

The patient was taking food satisfactorily until the tenth day, when he suddenly started to vomit. For the next three days he vomited everything given him. A small barium sulfate meal failed to pass through the stoma.

An emergency operation was performed on the thirteenth postoperative day. Numerous adhesions were found both in the duodenal region and about the stoma. The adjacent jejunum was covered with adhesions, which made it appear to be a part of the mesocolon. It seemed apparent that separation of the adhesions would be followed only by their reformation and further obstruction. A jejunoplasty was performed without further loss of time. The stoma was found to be adequate and not ulcerated. The jejunum, however, was densely adherent to the mesocolon for at least 4 cm. Recovery was uneventful, and the patient is now well except for an abdominal hernia.

CASE 4 (group 3).—W. K., 34 years of age, entered the hospital on Dec. 18, 1934, complaining of symptoms of duodenal ulcer of eighteen years' duration, for which a gastroenterostomy had been done elsewhere nine months before. The duodenal ulcer was cauterized. He was treated with a medical regimen until November 1935, when he again entered the hospital because of pain, weakness, fainting and hematemesis.

A second operation, a Billroth II subtotal resection, was done on Dec. 20, 1935. As his gastroenterostomy was working satisfactorily and no marginal ulcer was present, a subtotal resection of the stomach, including the duodenal ulcer (but with the gastroenterostomy left) was performed. Two weeks later signs of obstruction appeared, which eventually became complete, as no barium would pass the gastroenterostomy stoma.

A third operation, a jejunoplasty, was done on Jan. 25, 1936, thirty-six days after the second operation. Exploration showed that the stomach had rotated in such a manner that the loops of the jejunum were twisted and obstructed at the stoma, apparently owing to the loss of the gastrohepatic ligament after the gastrectomy. A jejunoplasty was immediately done; the patient made a satisfactory recovery, and emptying of the stomach was again normal. He was relieved for a time but about a year and a half later began to show symptoms of a marginal ulcer.

The fourth operation, a radical subtotal gastrectomy (Mayo-Polya) was done on Oct. 14, 1937. A marginal ulcer was found on the posterior wall of the jejunum, adjacent to the stoma. The patient made an uncomplicated recovery and is in excellent condition at the time of writing, with a total gastric acidity of only 13. It is still too early to know what may happen next. If he should have another ulcer, as there is no more stomach to resect, it may be visualized if necessary through another jejunoplasty.

In this instance a long-standing, perfectly functioning gastroenterostomy ceased to function after the distal end of the stomach was removed. It illustrates a type of mechanical obstruction in which there was nothing intrinsically wrong with the anastomosis, because it had previously functioned perfectly. It is not improbable that the same situation frequently occurs after an original gastroenterostomy, although no abnormality may be found at operation or autopsy.

JEJUNOPLASTY AS AN APPROACH TO MARGINAL ULCER AND  
FOR ENLARGEMENT OR CLOSURE OF  
THE GASTRIC STOMA

Although some form of subtotal gastrectomy is now universally recognized as the method of choice for the treatment of gastrojejunal or jejunal ulceration which has failed to respond to medical treatment, we believe that when more radical surgical treatment is contraindicated jejunoplasty offers many advantages over any other method with which we are familiar. The jejunoplasty readily visualizes the ulcer, which may be



Fig. 7.—First part of the jejunoplasty complete (approach for the removal of a marginal ulcer).

dealt with by excision or cauterization without disturbing the anastomosis and, more important, without the danger of narrowing the intestine or the stoma (fig. 7).

*Enlargement of Stoma (Gastrojejuno-plasty).*—When the stoma is found to be too small because of faulty technic or because of contraction in the presence of or after excision of a marginal ulcer, it may easily be enlarged as a final step in the jejunoplasty. This is accomplished by carrying a vertical incision through the stoma from the summit of the jejunal incision (fig. 8). A new center is chosen for closing the entire



incision so as to interpose gastric tissue between the ends of the divided stomal ring. In closure more tissue is taken up on the longer side with each stitch (figs. 9 and 10).

An illustrative case is reported.

CASE 5.—A. A., a man aged 37 years, in 1924 underwent a posterior gastro-enterostomy because of a densely adherent duodenal ulcer. Six months later symptoms of marginal ulcer developed. Conservative treatment resulted in improvement. In 1929 a subtotal resection (Mayo-Polya) was carried out because of partial obstruction of the stoma by a jejunal ulcer and evidence of persistence of the duodenal ulcer. In November 1931 a second marginal ulcer developed, which was treated medically with varying relief. In January 1938 the patient returned, suffering from severe pain and 90 per cent retention. In February 1938,

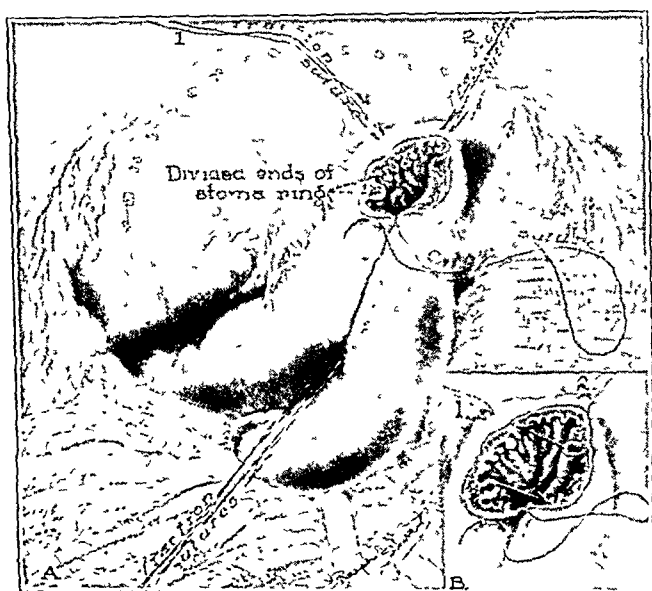


Fig. 10.—A, closure of the anterior wall of the jejunum and the stomach by staggering the suture line and interposing the gastric wall between the ends of the divided stoma to increase its size. (A longer stitch puckers the long side.) B, view of the stomal ring, showing how the increased size is obtained.

at the third operation, dense adhesions were found about the stoma, colon and jejunum. The jejunum was distended proximal and distal to the anastomosis. On exposure of the stoma through the jejunoplasty incision, it was found to be very small and contracted, with a small ulcer on its posterior view. The ulcer was cauterized, and the stoma was enlarged by means of the gastrojejunoplasty. Convalescence was uneventful, and there is no retention.

*Closure of the Stoma.*—In rare instances, because of recurring jejunal ulcer, it may be thought desirable to close the stoma and restore the original continuity of the bowel rather than to subject the patient to a subtotal gastrectomy. The jejunoplasty incision permits this restoration without the arduous dissection or resection which may be necessary to

undo the anastomosis. The stoma is delivered into the jejunostomy incision. The mucous membrane of the ring margin is excised. The margin of the gastric mucous membrane and the muscularis mucosa is dissected free until it can be conveniently united across the stoma by means of a double row of sutures everting the mucous membrane into the stomach (fig. 11). The muscle layers of the stomach and the jejunum are then brought together with interrupted silk sutures placed at right angles to the long axis of the original opening. These sutures do not penetrate the jejunal mucosa, which is usually so well approximated as to require no further suture. Closure is greatly facilitated by the

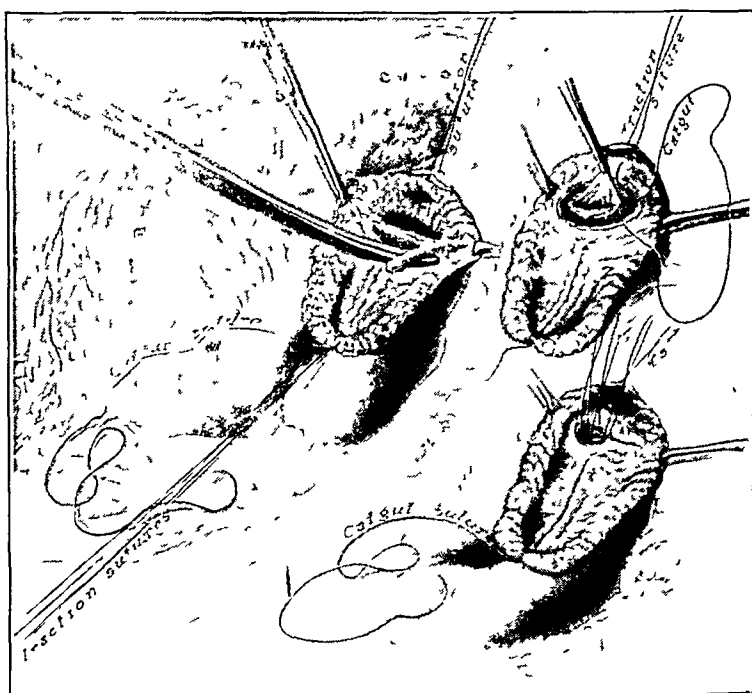


Fig. 11.—Complete closure of the gastric stoma from within the intestine (approach and closure as in figures 1 and 2). The mucous membrane covering the rim of the stoma is excised, exposing a wall made up of: (1) the muscularis mucosa of the stomach; (2) the combined muscle of the stomach and jejunum, and (3) the mucous membrane of the jejunum. The muscularis mucosa is detached from around the stoma and everted into the stomach by a Connell stitch of catgut. The muscular layer is closed with interrupted silk in the direction in which the stoma was originally made. These stitches approximate but do not penetrate the firmly attached jejunal mucosa, which falls together as the muscle is approximated and usually does not require a separate suture.

assistant's placing a hand behind the stomach and fully delivering the stoma into the field. The jejunoplasty is completed. Wherever closure is contemplated, it is essential to plan for a sufficiently long anastomosis of the jejunum to prevent the stitches about the closed stoma from

encroaching on the lumen of the intestine. *Under all other circumstances the anastomosis should be as short as is consistent with the correction of the mechanical difficulty, so that the alkaline duodenal excretions will continue to bathe the stoma and so minimize the hazard of jejunal ulceration.*

There has been considerable discussion as to just how jejunoplasty relieves obstruction. Clinically we believe that the condition presented is not unlike that of a double-barreled colostomy. Little or no intestinal contents may pass down the distal loop. If the septum is divided by a spur crusher it is almost impossible to prevent the fecal stream from passing downward. This is due not only to the restoration of the continuity of the intestine but to the fact that the peristaltic waves are passed on to the distal segment.

Experience has shown that if at least seven days has elapsed after a gastroenterostomy or other anastomosis, the circulation of the jejunum is adequate so that a jejunoplasty can be safely done.

#### SUMMARY AND CONCLUSIONS

Obstruction following gastrojejunostomy or subtotal gastric resection may be due to one of some ten causes, which are discussed.

The analysis and conservative treatment of obstruction due to certain of these causes are outlined.

The operative treatment and the position which jejunoplasty occupies in this treatment are discussed.

Suggestions are offered as to the value of jejunoplasty in cases of acute perforated marginal ulcer and the chronic obstructions.

We wish to state that we do not expect jejunoplasty to be a substitute for partial gastric resection in the treatment of marginal ulcer. We think, however, that it will be of value when, for any reason, the latter operation is contraindicated. It should be of special value when a marginal ulcer has developed after gastric resection and occasionally in the closure of a perforated jejunal or gastrojejunal ulcer, in which it is so important to relieve any associated obstruction or to avoid producing an obstruction in closing the perforation.

We feel that jejunoplasty is a life-saving measure in cases of acute obstruction which fails to respond to conservative therapy and requires reoperation. In addition, it would seem to be the operation of choice in that it restores and retains, with the minimum of surgical handling, conditions favorable to the eventual welfare of the patient by correction and mechanical perfecting of the initial operation.



## ABSTRACT OF DISCUSSION

DR. ARTHUR W. ALLEN, Boston: Malfunctioning stoma is not as common as it used to be. There are various reasons besides those that Drs. Hoag and Saunders have pointed out. Today the patient is better prepared; operative technic is better, and there is a better and more careful selection of the operation in the individual case. Probably the greatest single factors are the increasing knowledge of biochemistry and the correction of biochemical faults both before and after operation.

The operation which Drs. Hoag and Saunders have advocated is ingenious and undoubtedly will find a place in the treatment of malfunctioning stoma, possibly in the management of marginal ulcer. I believe, however, that although this operation is far superior to enteroenterostomy between the two limbs of a gastroenterostomy stoma it may have some of the same disadvantages. All who have investigated malfunctioning stomas have been aware of the tremendous reaction in the operative field and the tremendous amount of dissection necessary to expose the limbs of the anastomosis. Strangely enough, the patients, probably because they have become tolerant to surgical treatment owing to their previous operations or because their peritoneal cavities have been immunized to some extent, stand this sort of procedure surprisingly well, and the mortality associated with "messing around" in this region is not as great as one would expect.

The thing that bothers me is that one is undoing or upsetting a carefully planned procedure which one has done before, and if the results of that procedure are changed too much by any subsequent operation, the end result is not what one hopes it may be. Death may not occur, but there may be a situation which will be conducive to the same trouble encountered after enteroenterostomy, that is, ulcer at the stoma.

I think that the Abbott-Rawson tube recommended in Philadelphia, particularly by Dr. Ravdin, put down through the stoma into the distal limb of the jejunum, through which the patient may be fed early after operation, should be mentioned; it is a very important instrument which can be used for a badly depleted patient whom one wishes to feed immediately or as soon as the stage of physiologic ileus has passed. One can accomplish this early feeding by a jejunostomy at the time of operation, but the tube, I believe, eliminates the necessity of a jejunostomy at the time of operation. This tube, however, does not help in the type of case which Drs. Hoag and Saunders have described, which I believe presents an important surgical problem.

I have done a number of jejunostomies to feed patients with malfunctioning stomas, and I shall summarize the case records of 3 of these patients.

The first was a man 64 years of age. He had an obstructing duodenal ulcer of long standing, with chronic nephritis. He had an extremely thick, fat transverse mesocolon. He had an enormous omentum. I did not feel that I was justified in doing a gastric resection. I thought that the patient should be treated by gastroenterostomy. A gastroenterostomy was done. There was failure of function because of persistent obstruction. Nine days after the gastroenterostomy a jejunostomy was done, and twenty-five days after the gastroenterostomy he was able to pass material through the stoma. Thirty-five days afterward he was discharged in good condition. He was well and had no symptoms six months later.

The second patient had had recurrent severe massive hemorrhages. He had been operated on ten years previously by the late Dr. D. F. Jones, who had done almost exactly the same operation which Drs. Hoag and Saunders have described, ending with a two limb gastroenterostomy stoma which Dr. Jones called the pants-

leg gastroenterostomy. This patient continued to bleed. He did not have a jejunal ulcer, which is in favor of the contention of Drs. Hoag and Saunders, but he had severe gastritis and repeated massive hemorrhages due to this condition.

I did a subtotal resection, but there was failure of function. Twelve days afterward I did a jejunostomy, and I had to use a great deal of self control to wait forty-two days for that to function, but it functioned perfectly. He is well and asymptomatic, and he has the kind of anastomosis that I intended for him to have in the end.

This man had to have a posterior anastomosis owing to the fact that his jejunum had an extremely short mesentery, and I felt that in spite of the fact that he had a torn-up, thready mesentery in his mesocolon the posterior anastomosis would be better. That is the reason he had malfunction.

This shows how careful one must be in doing a jejunostomy. I have made all of the mistakes in doing jejunostomies for feeding both before and after operation. A long whistle tip no. 16 French catheter is put into the jejunum, which has been exposed through a good incision to determine the exact loop of the jejunum which will lie comfortably in the left upper quadrant of the abdomen. The catheter is held by two simple purse string sutures, and a little omentum is put around it. The catheter is not fixed to the abdominal wall except by a suture passed through the edge of the skin. I have seen jejunostomies of this type, performed for feeding, function for months in cases of cancer of the stomach.

The third patient was a man aged 42 who should have had a resection. He had a huge ulcer of the duodenum, which was badly infected. I did a gastroenterostomy. There was failure of function. Eight days afterward I did a jejunostomy, and function began thirty days after the original operation. The patient is well six months later.

These 3 instances illustrate how long one may keep a jejunostomy functioning.

Dr. Howard Clute, of Boston, has permitted me to mention a patient of his, a man on whom he did a jejunostomy for feeding twenty days after a subtotal gastrectomy with malfunction. Thirty-nine days after the original operation this stoma functioned perfectly, and the man has remained well.

Dr. Roscoe Graham, of Toronto, Canada, has had a similar case, in which restoration of function took thirty-five days.

When one considers how well one can manage a jejunostomy, take the fluid aspirated from the stomach through a Levine tube, and feed the patient properly through the jejunostomy, one realizes that the stoma will eventually function.

DR. E. E. MUNGER JR., Spencer, Iowa: My question concerns the use of the duodenal tube in gastric operations. I have employed it with satisfaction in the Billroth I resection, in which, owing to the peculiarity of the suture line, I have felt that there is even greater indication for its use than in the gastrojejunostomies. I should like to have on record an opinion relative to this and also to know whether there is any recognized contraindication to this use of the duodenal tube.

DR. HOWARD K. GRAY, Rochester, Minn.: Undoubtedly, this type of operation is of considerable value in many instances. There are certain conditions, however, in which it would seem impossible to apply this procedure, because of the tremendous amount of inflammation that may be found in the region of the jejunal loops. To perform this operation satisfactorily it is necessary to isolate and satisfactorily expose not only the two loops but that portion of the jejunum which is adjacent to the stomach. Occasionally the stoma may be retracted through the opening in a

markedly thickened transverse mesocolon, and under such circumstances it might be impossible to accomplish a satisfactory operation such as Drs. Hoag and Saunders have described.

Drs. Hoag and Saunders have mentioned particularly those cases in which there is intractable retention occurring immediately after operation. In my experience the patients in whom gastric retention develops immediately after operation are those who are less likely to progress satisfactorily by themselves, whereas the majority of those in whom retention develops on the ninth or tenth day are patients who will improve spontaneously provided positive water and electrolyte balances are maintained.

DR. CARL L. HOAG, San Francisco: Regarding jejunostomy for the relief of these obstructions, I agree with those who have spoken that if one could be assured that the bowel would function this would be the procedure of choice. However, my experience has not been as satisfactory as that of Dr. Allan. I have had a number of these patients; 1 died with a massive infection of the abdominal wall and another of continued obstruction, the stoma never resuming function even though he lived thirty-five days. Although the records are significantly silent regarding such failures, I doubt that I am the only one to have had them.

Regarding the points brought up by Dr. Gray about the technic of jejunoplasty, of course the more experience one has the easier it becomes. It is not necessary to break up all the adhesions about the anastomosis if there are many. We identify the limbs of the intestine, open it as near the stoma as possible and then follow the lumen of the jejunum around, cutting and pushing aside only enough adhesions to permit approximation of the edges of the intestine. We pay no attention to the others. In every instance yet encountered this could be done with little difficulty.

If one should be so unfortunate as to encounter a case in which the jejunum has been attached to the stomach with 180 degrees of rotation, this operation will take care of that situation as well, because we have demonstrated it experimentally on numerous occasions.

We feel that we can say without reservation that, whatever the ultimate frequency of marginal ulcer may prove to be, this procedure will promptly relieve the obstruction for which it was designed.

There may be some doubts as to how frequently obstructions occur. Any one who had stood with me in my booth in the Scientific Exhibit for the past three days and had interviewed literally hundreds of physicians who are a cross section of the membership of this Association and who came in for unofficial consultation about this problem would have a better understanding of the frequency and seriousness of this complication and would feel a little differently about some of the points expressed.

## Foreword to Article by Dr. Mohs

This paper presents a method for the treatment of carcinoma which is localized to an accessible region of the body. It does not give the answer as to the cause of cancer, nor does it eliminate surgical intervention or radium or roentgen therapy in the treatment of the disease. The method is the result of eight years of work in the laboratory and four years of clinical experience, during which time well over 600 cases have been observed and the results of treatment carefully analyzed.

The escharotic agent may be one of several, and the base may be one of many. Over two hundred different bases were studied, and many were suitable. The combination used may be varied, with equally good results. In the last analysis it is the method of control rather than the chemical agent itself that promises an advantage.

The advantage of this treatment is that it is a refined, carefully controlled method. The diagnosis is always based on a histologic study of the tissue removed. The progress in its removal is controlled histologically; normal tissue is spared, and extensions of the carcinoma can be recognized and removed with some assurance of adequacy. It is not dependent on clinical judgment or on a rule of thumb. The depth of action of the escharotic agent can be controlled by the thickness of the paste applied. Because of the resulting coagulation necrosis there is a minimal reaction, and no danger of disseminating either the tumor cells or an infection.

The method presupposes certain qualifications of the prescribing physician. An accurate knowledge of gross, topographic, pathologic and histologic anatomy is essential for the application of the escharotic agent, and the recognition of the histologically normal and pathologic tissue must be ready if accuracy in the therapy is to be attained.

This method, unless it is controlled as suggested, will be gross, crude and unrefined—no better than using a large soldering iron, sacrificing normal tissue and waiting to see whether metastases occur. From my clinical experience I consider this method a valuable adjunct in combating accessible cancers. It should be added to roentgen therapy, radium therapy and operation as another therapeutic weapon to this end. Time will assign to it the proper place and value.

ERWIN R. SCHMIDT, M.D.

Professor of Surgery, University of Wisconsin.

## CHEMOSURGERY

### A MICROSCOPICALLY CONTROLLED METHOD OF CANCER EXCISION

FREDERIC E. MOHS, M.D.

MADISON, WIS.

The object of this study was to develop a method for removing accessible cancers under complete microscopic control. The only practical way of obtaining this microscopic control involved the chemical

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This project was aided by the Thomas E. Brittingham Fund, the Jonathan Bowman Memorial Fund and the Wisconsin Alumni Research Foundation.

From the Department of Surgery, Wisconsin General Hospital, and the McArdle Laboratory for Cancer Research, University of Wisconsin Medical School.

Valuable help in this work has been given by Prof. M. F. Guyer, of the department of zoology; Dr. E. R. Schmidt, of the department of surgery; Drs. R. L. McIntosh and O. H. Foerster, of the department of dermatology; Dr. W. E. Sullivan, of the department of anatomy, and Dean W. S. Middleton, chairman of the cancer committee, of the medical school of the University of Wisconsin.

fixation of the suspected tissues *in situ* so that the fixed tissues could be excised layer by layer and subjected to thorough systematic microscopic examination as a guide to treatment. The materials and technics for producing fixation *in situ* were worked out in animals by Guyer and me.<sup>1</sup> The main advantage of this chemosurgical treatment is that it enables the sure removal of a given cancer, including all its irregular and unsuspected extensions, with minimal destruction of normal tissue.

#### IN SITU FIXATIVES

In order to obtain accurate control of tissue fixation over a wide range of depths a special plastic fixative preparation was devised. For the fixative chemical itself zinc chloride was finally selected, not only because its excellent fixation preserves gross and microscopic tissue structure but because it is nontoxic, can be accurately controlled when incorporated in a suitable base and, moreover, since it has little effect on the intact skin, is safe to handle.

The special base was designed to have (1) a low affinity for the fixative chemical, allowing its easy exit from the paste into the tissues, and (2) a capillary structure enabling passage of the chemical from all levels of even very thick applications, making possible regulation of the depth of fixation over a wide range by merely altering the depth of application.

These properties were imparted to the base by the combination of two types of substances: (1) a "permeant," a finely granular, insoluble material of mineral origin having little affinity for the solution of zinc chloride and providing multiple interfaces of correct size to produce high permeability, and (2) an "agglutinant," an adhesive, cohesive, organic material of plant origin added in just sufficient quantity to keep the solution of zinc chloride from settling to the bottom of the container on standing. The following formula is satisfactory:

#### Fixative Z-108a

Stibnite, 80 mesh sieve.....	40.0 Gm.
Sanguinaria canadensis.....	10.0 Gm.
Zinc chloride, saturated solution.....	34.5 cc.

As was pointed out previously,<sup>1</sup> this preparation produces excellent fixation, so that the microscopic structure of the tissues is retained with little change except for some cell shrinkage and concentration of cytoplasmic and nuclear material.

1. Mohs, F. E., and Guyer, M. F.: Pre-Excisional Fixation of Tissues in the Treatment of Cancer in Rats, Cancer Research, to be published.

## TECHNIC

Though the proper type of fixative is invaluable for controlled fixation, the essential feature of the chemosurgical method lies in the microscopically controlled technic by which cancer tissue is removed.

The main steps in the technic are: 1. Application of the fixative agent to the surface of the tumor, the dose depending on the penetration desired. 2. Surgical excision of the fixed layer of tissue twenty-four hours later. 3. Location and mapping of the cancerous areas in relation to body landmarks by examination of microscopic sections made from the removed tissues. 4. Daily repetition of this process, only cancerous areas being treated, until a microscopically noncancerous plane is reached. These steps are more fully described in the following paragraphs.

In preparing the surface of the tumor for the first application of the fixative, all loose crusts, scales and detritus are removed. To skin-

TABLE 1.—*Depth in Millimeters of Penetration by Fixative Z-108a*

Depth of Application, Mm.	Diameter of Area, Cm.							
	0.3	0.5	1.0	1.5	2.0	3.0	5.0	10.0
0.1	1.0	1.2	1.5	1.9	2.1	2.2	2.3	2.3
0.3	1.2	1.4	2.0	2.4	2.9	3.2	3.5	3.6
0.5	1.4	1.6	2.4	3.2	3.8	4.0	4.2	4.3
0.8	1.7	1.9	2.9	3.9	4.5	4.7	4.9	5.0
1.0	1.9	2.2	3.4	4.4	5.1	5.4	5.6	5.7
1.5	2.1	2.8	5.0	5.6	6.4	6.9	7.3	7.7
2.0	2.4	3.2	6.3	7.0	7.8	8.5	9.0	9.4
3.0	2.6	3.5	7.0	8.0	8.7	9.3	9.7	10.0

covered areas a keratolytic, such as dichloroacetic acid, is applied, making it possible to scrape off the keratin, which otherwise would form a barrier to the zinc chloride.

The fixative paste is then applied to the surface of the tumor. If the neoplasm is located in a favorable position and is not too large, it is often possible to calculate the dose so that the main mass of tumor can be removed twenty-four hours later. The depth of penetration depends mainly on two factors: (1) the depth of application of the fixative paste and (2) the area of application (table 1).

There are, however, many additional factors which may alter penetration. Some types of tissue, such as heavily keratinized squamous cell carcinoma or heavily pigmented melanosarcoma, offer increased resistance to the passage of the fixative, owing to the high content of keratin and melanin respectively. Penetration along the longitudinal axis of a muscle bundle is greater than penetration perpendicular to this axis. Decreased circulation, such as that caused by radiation endarteritis, vascular occlusion or scarring, accelerates penetration, while

increased circulation, such as occurs with inflammation, reduces penetration. Secretions and exudates dilute the fixative, reducing penetration. Non-air-tight dressings when the atmospheric humidity is low decrease penetration, owing to excessive withdrawal of water from the fixative preparation. The effective penetration through loose-knit tissue is less than that through firm tissues, owing to the greater capacity for swelling in the former.

This multiplicity of factors influencing penetration makes experience and constant practice important in the accurate control of fixation. In practice, penetration tables are not used, the dose being determined by a consideration of all the variables influencing penetration in a given instance.

The applied fixative is held in place by a cotton dressing. Since alterations in atmospheric humidity alter penetration and since low humidity causes excessive hardening of the tissues, it is necessary to make the dressing air tight. This is done by covering the first layer of cotton with a second, spread with petrolatum. This is then securely taped in place.

Penetration usually is complete in eighteen hours, but for convenience the fixative is left in place for about twenty-four hours. If the lesion is large or is in a highly sensitive region, there may be periods of discomfort. While most patients easily tolerate the stinging type of pain, it is customary to order an analgesic, which is to be given at the patient's request.

At twenty-four hours the first layer of tissue is excised with a scalpel. Since the tissue has been killed and fixed, there is no pain from this operation. There are few if any bleeders, and when these are encountered they are rapidly controlled by applying a small square of fixative-impregnated gauze under momentary pressure. By this means bleeding from arteries as large as the external maxillary and the superficial temporal artery can readily be stopped.

At the first excision the grayish white, caseous cancer tissue is usually grossly detectable, so only a specimen for histologic diagnosis is sectioned (fig. 1*A*, first excision). Another application of the fixative is then made, in a dose dependent on the depth of fixation desired.

If at the next excision it is considered possible that most of the cancer may have been fixed, a layer of tissue is excised in such a manner that frozen sections may be made and the entire plane studied microscopically (fig. 1*A* and *B*, second excision). Areas of cancer thus found are located on maps drawn both on paper and on the lesion itself (with mercurochrome or india ink). The lesion is kept moist for the few minutes required to prepare and examine the frozen sections. Then fixative is applied to the areas proved still to contain cancer.

The following day the fixed tissues are again excised and subjected to microscopic study. The process is then repeated until a completely noncancerous plane is reached.

From three to nine days is required for the remaining thin layer of fixed tissue to separate. Often it is necessary to cut the heavier fibrous strands causing adherence of this tissue. Blood vessels heal across, and therefore bleeding rarely occurs. The upper surface of this layer may also be sectioned if the occasion demands.

The granulation tissue exposed as the final layer of fixed tissue separates is remarkably vascular and is highly resistant to infection. The lesion at this stage is dressed with scarlet red-oxyquinoline sulfate gauze, as described by Bettman.<sup>2</sup> Defects quickly fill in, and epithelization is surprisingly rapid. The resulting scars are soft and pliable. The

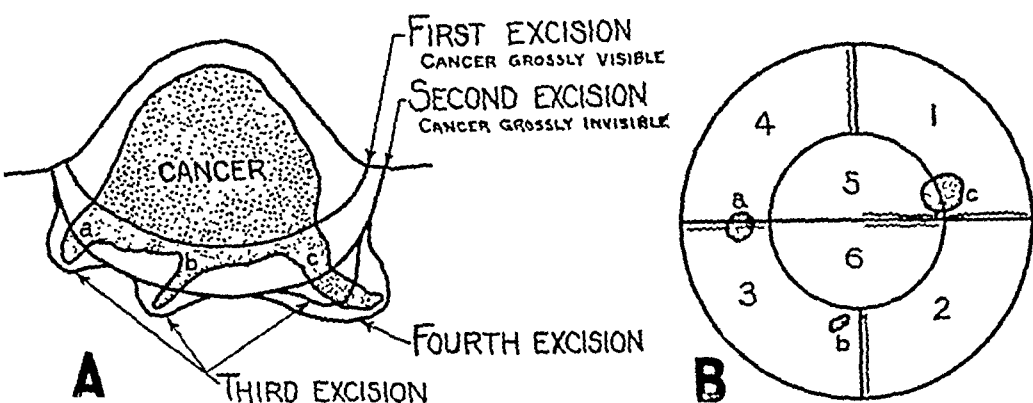


Fig. 1.—Diagrams showing the technic for locating cancer microscopically during the course of extirpation. The shaded areas represent cancer. *A*, side view of the lesion, showing deep extensions (*a*, *b* and *c*), and the four planes of incision. *B*, map of the top view of the second excised layer, showing how the deep extensions (*a*, *b* and *c*) are located microscopically by examining the sections made through the under surface of each specimen. In this example four excisions were required to reach a completely cancer-free plane.

area remains pink for several weeks and then fades out to approximately the color of the surrounding skin.

#### INDICATIONS FOR CHEMOSURGERY

Any neoplasm which is readily accessible from the surface of the body or which can be reached through a normal, a pathologic or an artificial orifice may be treated chemosurgically if a technic can be devised to hold the fixative preparation in place. Of course, involvement of vital structures or distant metastasis may be contraindicatory

2. Bettman, A. G.: A Simpler Technic for Promoting Epithelization and Protecting Skin Grafts, *J. A. M. A.* **97**:1879 (Dec. 19) 1931.



factors. Brief consideration of the more important lesions which may be treated follows.

*Carcinoma of the Nose.*—Nasal carcinoma of both the basal cell and the squamous cell type frequently shows a deep-growing, invasive type

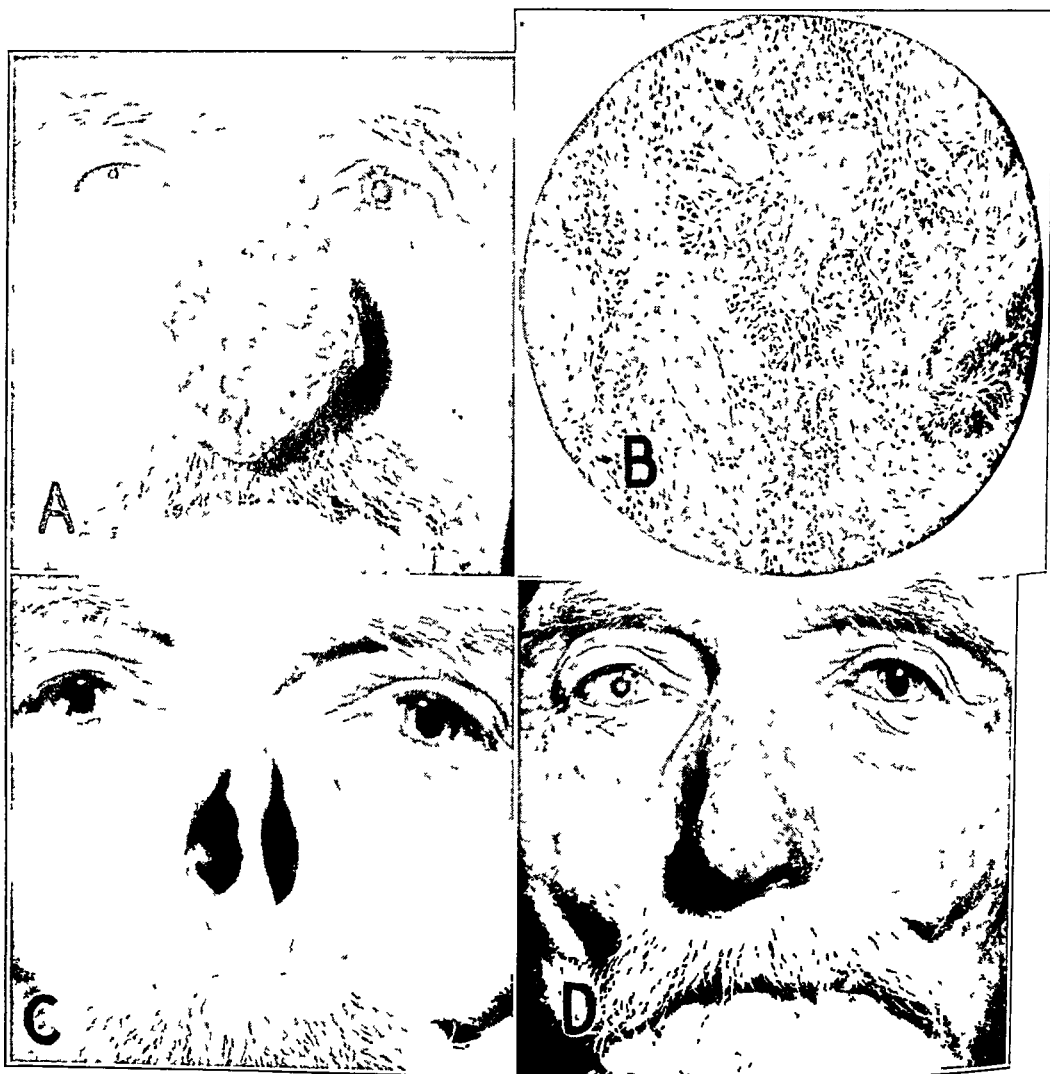


Fig. 2.—*A*, squamous cell carcinoma, grade 2, involving almost the entire nose and the adjacent cheeks. There was a metastatic nodule near the left inner canthus. *B*, microscopic appearance of tissue fixed in situ (upper three fourths of photomicrograph) as compared to tissue fixed in vitro in Bouin's solution (lower one fourth). Zinc chloride fixation produces cell shrinkage with resultant intercellular clefts, increased nuclear basophilism and pyknosis and increased cytoplasmic eosinophilism. *C*, appearance of the defect six months after removal of the primary and metastatic lesions. *D*, prosthetic nose indicated because of advanced age (91 years). The patient remains free from cancer after four and one-half years

of spread. This is especially true in the fusion planes between the nose on the one hand and the lip and cheeks on the other. Moreover, the similarity in consistency of the fibrocartilaginous nasal tissue and cancer tissue makes their distinction by palpation difficult. These circumstances make impossible a diagnosis of the true extent of nasal carcinoma by ordinary examination. Hence, the microscopic control afforded by the chemosurgical technic makes for an unprecedented certainty of removal with a minimum of destruction of normal tissue. Of course, the destruction of the full thickness of the nasal walls results in a corresponding defect (fig. 2), but usually it is possible to avoid penetration through the nasal mucosa, and the cosmetic results are then

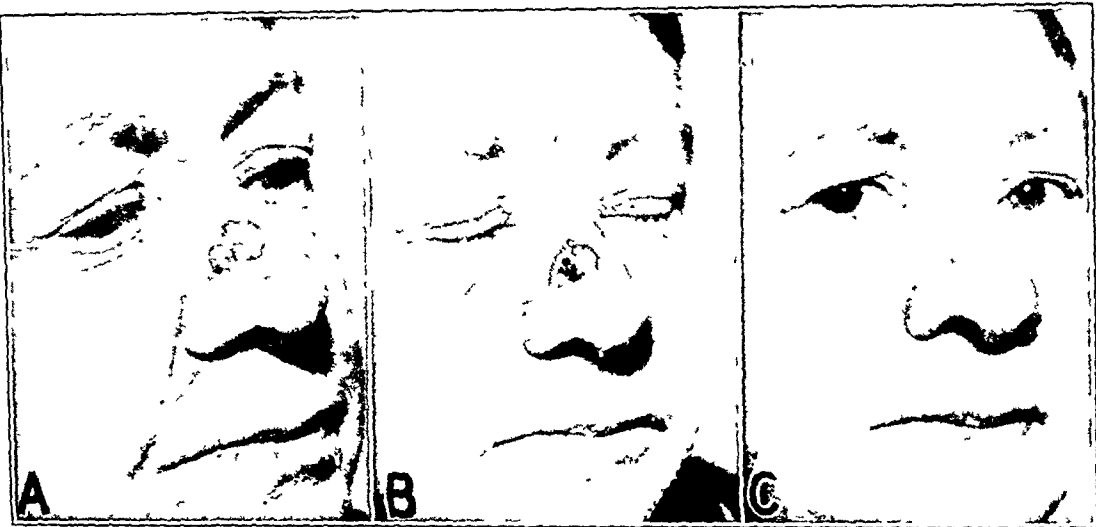


Fig. 3.—*A*, basal cell carcinoma measuring 14 by 16 mm. The white atrophic scar near the inner canthus resulted from radium treatment of a 6 mm. basal cell carcinoma five years previously. *B*, granulation tissue immediately after separation of the final layer of fixed tissue. Four days of chemosurgical treatment was required to reach a microscopically noncancerous plane. *C*, condition two months after treatment. The patient remains free from cancer after one and one-half years.

excellent (fig. 3). Septal and intranasal neoplasms may require the use of nasal packing and special dressings to keep the fixative in place.

*Carcinoma of the Ear.*—Aural cancer practically always comes in contact with a sheet of cartilage at an early stage, and, although cancer spreads readily along the perichondrium, it is unusual for it to penetrate through a layer of cartilage. This circumstance facilitates chemosurgical treatment, since it is necessary simply to remove all tissues down to the cartilage and then carry fixation peripherally until non-cancerous sections are obtained. A layer of cartilage is then removed

with the final layer of fixed tissue, and healing takes place with little defect (fig. 4).

If the cancer extends through the cartilage, the defect is usually grossly visible, and it is then necessary to carry fixation to the other side until noncancerous sections are obtained. Cancers extending inward along the canal may be followed in to the middle ear if necessary.

*Carcinoma of the Eyelid.*—This form of cancer is especially amenable to chemosurgical treatment, mainly because in this location it is impor-

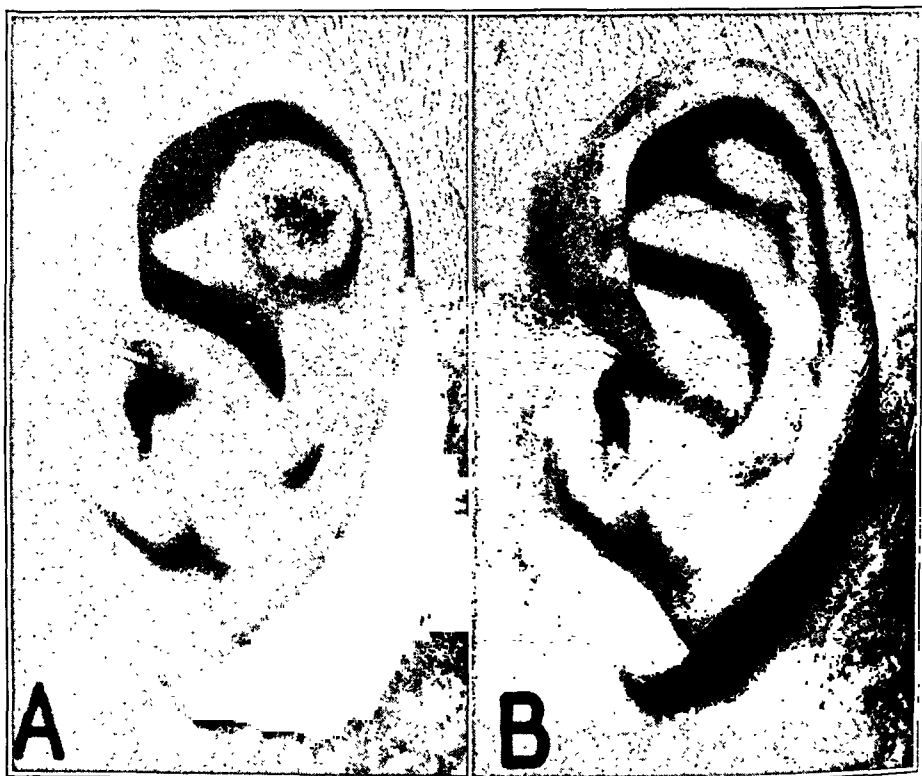


Fig. 4.—A, squamous cell carcinoma, grade 2, involving the outer surface of the ear. B, condition three months later. There is no evidence of cancer after three and one-half years.

tant to save a maximum of the surrounding normal tissue. The accurate control of fixation plus the protective reactions of tearing, chemosis and edema make it possible to remove portions of an eyelid or even an entire eyelid without damaging the eyeball. Healing occurs with surprisingly little defect (fig. 5) unless the lesion has extended deeply into the orbit, in which case corresponding defects occur (fig. 6). In extensive lesions it is common for the cancer to follow along the periosteum far into the orbit, and sometimes it extends through the

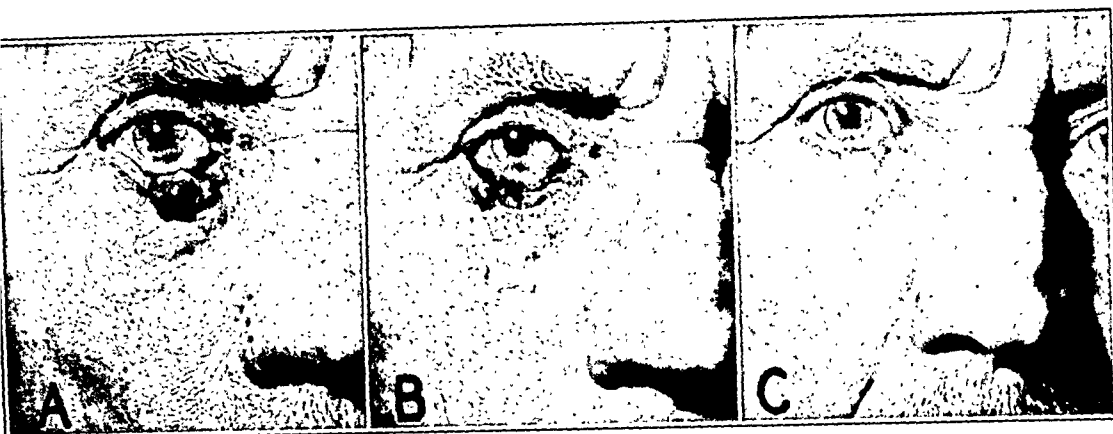


Fig. 5.—*A*, squamous cell carcinoma of the lower lid, including 3 mm. of the palpebral conjunctiva. *B*, condition after separation of the final layer of fixed tissue, eight days later. *C*, condition three months later. The patient remains free from cancer after one year.



Fig. 6.—*A*, basal cell carcinoma, kept in check *superficially* for ten years by numerous radium treatments. *B*, condition at completion of active treatment, showing the extensive deep spread of the cancer. Edema and chemosis are evident. The insert is a reconstruction of the actual mass of cancer, demonstrating the irregular extensions along the inferior and medial walls of the orbit, into the upper lid, onto the nasal bone and into the lacrimal fossa. *C*, defect three months later. There was no impairment of vision, but exposure of the conjunctiva required plastic repair of the lower lid. The patient remains free from cancer after two years.

bone into the maxillary, ethmoid or frontal sinuses. Under such circumstances it is necessary to remove the eye and carry fixation to a completely cancer-free plane.

*Neoplasms of the Face.*—These require no special consideration except for mention of the type of healing to be expected in various locations. Lesions of the forehead, even when very large, heal with little defect, although if they are near an eyebrow some retraction may occur (fig. 7). Lesions of the cheek heal well unless they are very deep, in which case slight puckering around the scar may occur. Lesions on the side of the neck heal with a narrow linear scar, which usually is barely visible.

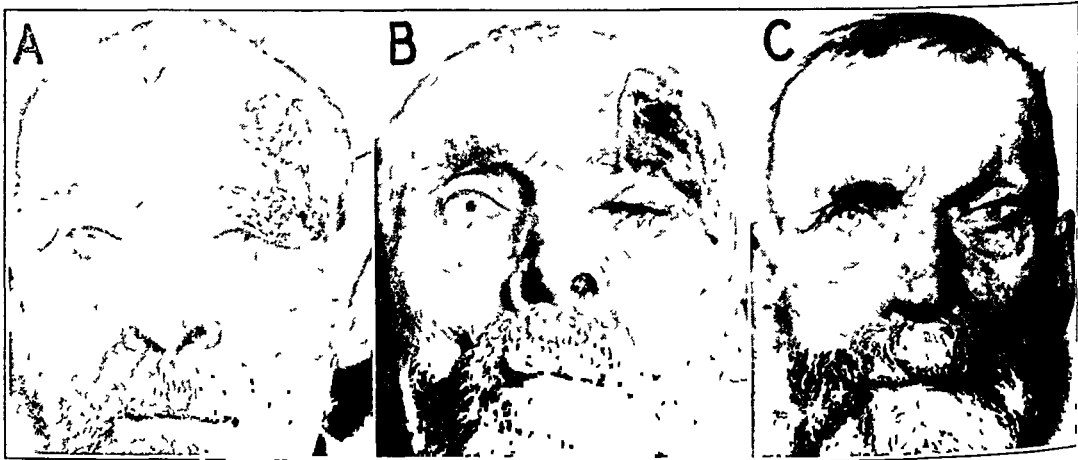


Fig 7—*A*, squamous cell carcinoma, grade 3, involving the temporal region and extending into the upper eyelid *B*, condition fifteen days later; note the granulations following separation of the final layer of fixed tissue. *C*, condition one year later. Scar contraction caused some retraction of the upper lid. The patient shows no evidence of cancer after three years

*Carcinoma of the Lip.*—This requires special care in applying dressings because of the constant movement and because of wetting by saliva and fluids. The orbicularis oris muscle affords a moderate degree of resistance to the spread of carcinoma, and the minimal amount of tissue removed by the chemosurgical technic allows healing with excellent cosmetic results (fig. 8). If in very extensive lesions too much lip is removed for good function, an immediate, simple plastic repair is desirable (fig. 9).

The danger of metastasis from cancer of the lip is an important consideration, especially with large or anaplastic lesions in which surgical resection of at least the submental and submaxillary nodes is indicated. If the nodes are already involved but are still freely movable, ordinary surgical resection is practiced. If the nodes are fixed

to the mandible and other surrounding structures and if the cancer has not demonstrably extended beyond the submental and submaxillary regions, it has been found effective to remove these nodes chemosurgically.

*Neoplasms of the Parotid Gland.*—These, including both carcinoma and mixed tumor, are excellent subjects for chemosurgical treatment, since sure removal of the tumors is accomplished with a maximum chance of saving the facial nerve. Carcinoma in the lower part of the gland usually can be removed with little or no nerve involvement (fig. 10), while lesions higher in the gland are more apt to eventuate in some degree of facial paralysis. Parotid fistulas may occur, but they invariably close promptly. The lack of encapsulation and irregular

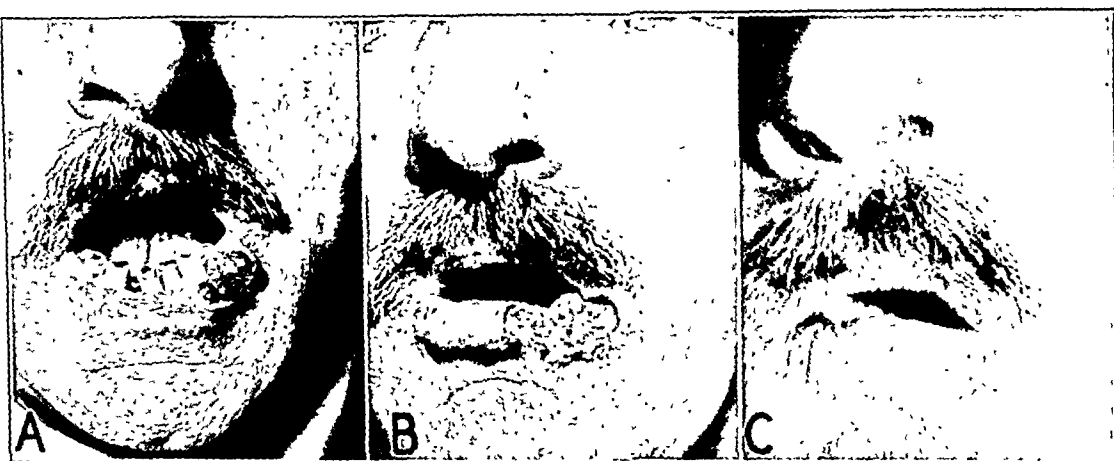


Fig. 8.—A, squamous cell carcinoma, grade 2, of the lower lip. B, condition seven days later, immediately after the final layer of fixed tissue was removed. C, condition one month later. The patient remains free from cancer after two and one-half years.

extension of the neoplasms of the parotid gland make the microscopic control of the chemosurgical method an invaluable factor in assuring complete removal.

*Carcinoma of the Mouth.*—This is amenable to chemosurgical treatment only when a suitable means for holding dressings in place can be devised. Cancers involving the palate and the upper alveolar ridge are easily treated chemosurgically with the aid of dental prostheses.

*Carcinoma of the Extremities.*—This most often involves the hands, though no part is immune. It is especially desirable to save as much as possible of the substance and function of the hands. By the chemosurgical method even extensive lesions which involve the bones and which ordinarily would require amputation may be removed with the

preservation of much useful function. The great variation in tissue arrangement and structure in the hand makes for great irregularity in outline of the tumor, so that the microscopic control is an invaluable

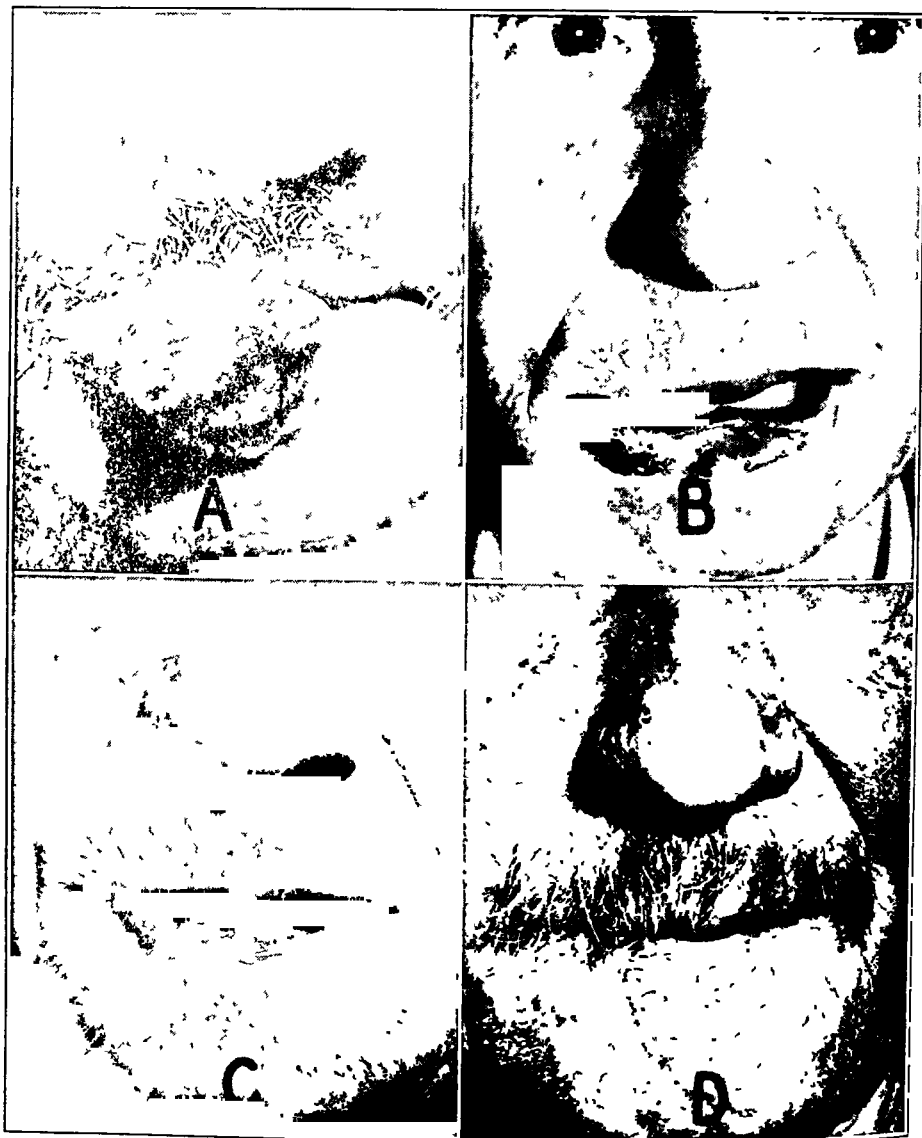


Fig 9.—*A*, squamous cell carcinoma of the lower lip, recurrent after radium irradiation and operation. *B*, condition immediately after separation of the final layer of fixed tissue. *C*, condition three weeks later. The lesion had healed, but there was insufficient structure for good function, so immediate plastic closure was made. *D*, condition four months later. There is no evidence of cancer after three years.

advantage. The frequency of metastasis from squamous cell carcinoma of the hand requires careful consideration of the cubital and axillary

nodes. The latter are amenable to chemosurgical removal if those affected are limited to the lower part of the axilla, but if they are too close to the axillary vessels the procedure is usually contraindicated.

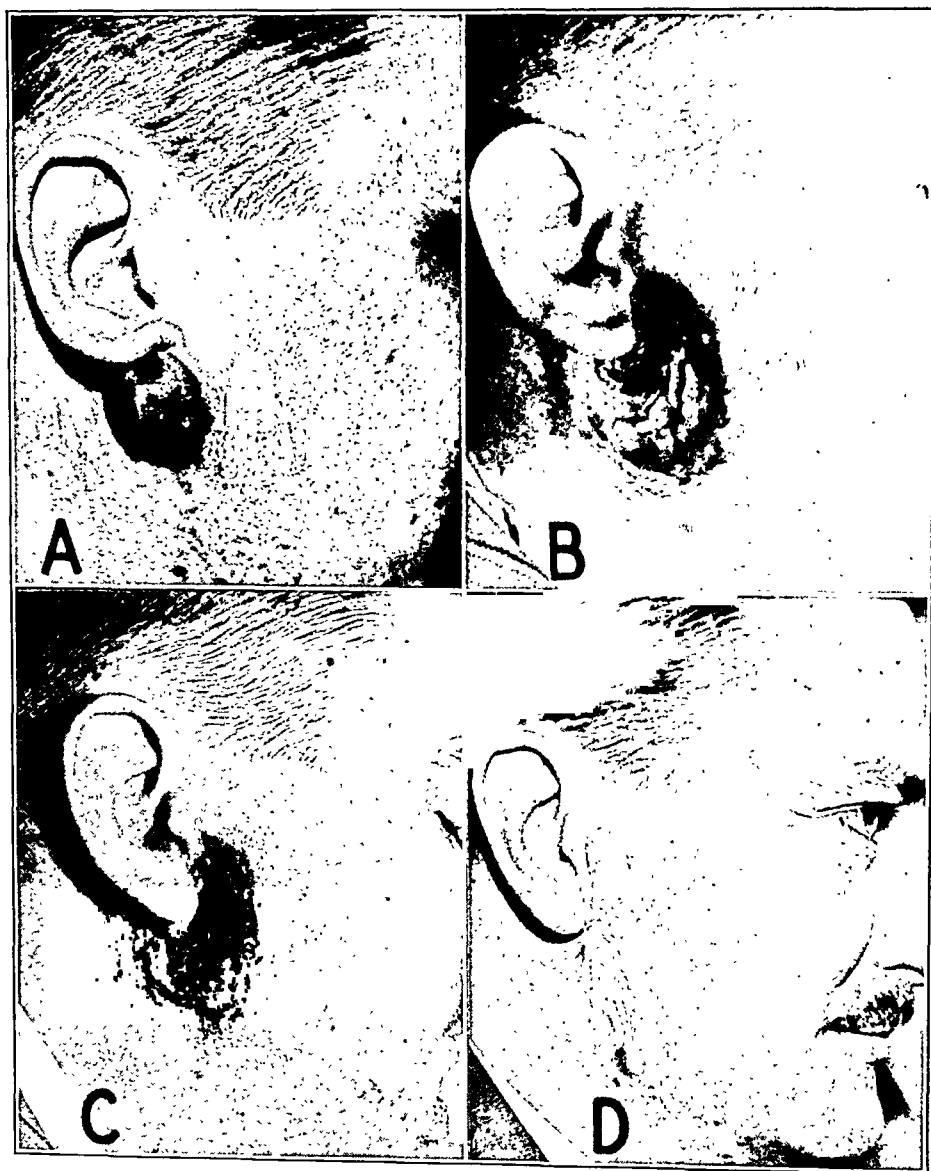


Fig. 10.—*A*, carcinoma of the parotid gland, showing an infected ulcerated protrusion from the main tumor mass, which was deeply situated. *B*, condition three weeks later, at which time a completely cancer-free plane had been reached at a depth of 2.3 cm. below the level of the skin. *C*, condition six days later, showing how rapidly defects fill in and close in after chemosurgical treatment. *D*, condition two years later, showing the scar and absence of facial paralysis. The patient remains free from cancer after two years.



Lesions on the soles may be removed, but if weight-bearing surfaces are involved the resulting scar may cause a moderate degree of discomfort on walking.

*Carcinoma of the Penis.*—This may be treated chemosurgically without obstruction to urinary flow either by the swelling during treatment or by scar contraction later. The entire prepuce and a rim of the glans were removed in 1 case without resultant obstruction.

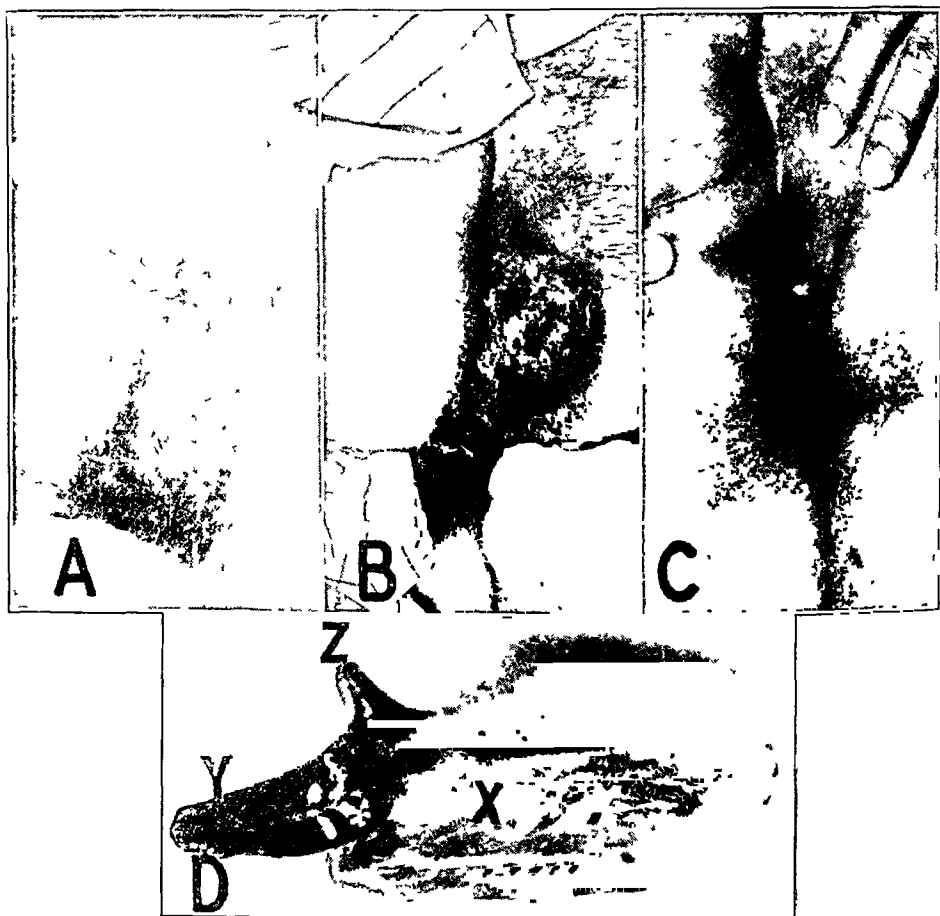


Fig. 11.—*A*, basal cell carcinoma, persistent after two years of radium treatment, involving the buttock, the anus and the lower part of the rectum. *B*, condition after removal of the final layer of fixed tissue. *C*, condition four months later. The lesion healed with only slight impairment of sphincter function. There was no evidence of cancer after one and one-half years. *D*, reconstruction showing the actual extent of the cancer in relation to the visible ulcer (*X-X*). Extensions up the anterior wall of the rectum (*Y*) and around the lateral surface of the external sphincter ani (*Z*) are shown.

*Carcinoma of the Buttocks, Anus and Rectum.*—Chemosurgical measures may be used if the lesion does not extend too far up the rectum. Treatment in the lower part of the rectum is carried on by means of packs to keep the dressing in place. Colostomy is not necessary, and trouble does not result from feces passing over the wound. The retention of sphincter function if the muscle is not extensively invaded is a further advantage of chemosurgical treatment of lesions around the anus (fig. 11).

*Carcinomas of the Vulva and Vagina.*—These may be removed chemosurgically, and healing is remarkably good. Close proximity or

TABLE 2.—Results of Treatment of 440 Consecutive Primary Malignant Lesions by Chemosurgery

Location	Type of Tumor	No. of Cases	Number Cured	Per Cent Cured
Buttocks, anus and rectum.....	Basal cell	3	3	100.0
Buttocks, anus and rectum.....	Squamous cell	2	1	50.0
Branchial cleft.....	Carcinoma	1	0	0.0
Breast.....	Carcinoma	3	1	33.3
Ear.....	Basal cell	20	17	85.0
Ear.....	Squamous cell	12	10	83.3
Eyelids.....	Basal cell	37	35	94.6
Eyelids.....	Squamous cell	11	10	90.0
Extremities and trunk.....	Basal cell	10	10	100.0
Extremities and trunk.....	Squamous cell	19	18	94.7
Face and head.....	Basal cell	87	87	100.0
Face and head.....	Squamous cell	40	37	92.5
Lip, lower.....	Basal cell	1	1	100.0
Lip, lower.....	Squamous cell	81	80	98.8
Lip, upper.....	Squamous cell	3	2	66.6
Mouth.....	Squamous cell, sarcoma and adamantinoma	5	2	40.0
Nose.....	Basal cell	69	67	97.0
Nose.....	Squamous cell	9	9	100.0
Parotid gland.....	Carcinoma	4	4	100.0
Parotid gland.....	Mixed	2	1	50.0
Penis.....	Squamous cell	2	1	50.0
Vulva and vagina.....	Squamous cell	4	3	75.0
All sites.....	Angioblastic endothelioma	2	2	100.0
All sites.....	Sarcoma	6	3	50.0
All sites.....	Melanosarcoma	7	5	71.4
Total primary lesions.....		440	409	93.0

involvement of the lower part of the urethra is not a contraindication. Carcinoma of the cervix would seem to be a possible candidate for chemosurgical treatment, but this will not be considered here, owing to insufficient data.

*Carcinoma of the Breast.*—As a chemosurgical problem this also awaits clarification. In this series, only 1 patient, a very poor surgical risk, was treated in the operable stage, and she remains free from cancer after three years. Recurrent lesions in the primary site are advantageously treated chemosurgically, but axillary metastases are not. After chemosurgical mastectomy the defect heals rapidly and well without plastic repair.

*Sarcoma, Melanoma and Other Malignant Tumors.*—These, as well as various benign neoplasms, may also be treated chemosurgically.

#### RESULTS

Considerations of space prevent me from undertaking in this paper a detailed analysis of the results in each tumor site and with each type of tumor. It is possible only to present in tabular form the results of treatment of 440 consecutive primary malignant lesions treated chemosurgically over a period of four years (table 2). Although each case is being actively checked for a period of five years, the follow-up is obviously incomplete as yet, since the last patients of this series were treated only in October 1939. Therefore, the follow-up period varies from one year to four and a half years. It may be mentioned in this connection, however, that if recurrence after chemosurgical treatment is to take place it manifests itself early, usually well within six months.

Of the 440 cancers treated chemosurgically, 409, or 93 per cent, showed no evidence of cancer when this paper was prepared. Since this group includes a large number of extremely advanced and even hopeless lesions and since over one third had been previously unsuccessfully treated by operation, roentgen therapy or radium therapy, it would appear obvious that such a high proportion of cures compares favorably with the results which would be expected from ordinary surgical and radiation methods. More thorough evaluation will be made in future articles concerning specific lesions.

#### COMMENT

A striking feature of a high proportion of cancers found at or near the surface of the body is the irregularity of their outlines. As Lathrop<sup>3</sup> has shown by reconstructions, there is a marked tendency for these neoplasms to follow along fascial planes, periosteum, perichondrium, perineurium, embryonic fusion planes, lymphatics and other routes offering reduced resistance to the spread of cancer. Often these irregular outgrowths from the main mass are undetectable by gross examination, owing to their small size or their similarity in consistency and appearance to the replaced normal tissue. The great value of the microscopically controlled method described here lies in its use to follow out and remove all of these extensions.

A further advantage of the chemosurgical method is that there is no such thing as "chemoresistance." While it is true that penetration is slower through tumors containing a high content of keratin, melanin

3. Lathrop, T. G.: *The Morphology of Certain Neoplasms as Demonstrated by Reconstructions*, Thesis for Doctorate in Medicine, University of Wisconsin Medical School, 1940.

or osseous tissue, there is no type of tumor which will not respond to chemosurgical treatment.

Technical advantages enable the chemosurgical removal of certain lesions otherwise inoperable because of large size, infection or difficult position. Furthermore, there are no failures in healing and no complicating infections. Should plastic repair of defects be required after chemosurgical removal of extensive lesions, the well vascularized tissue heals well, and breakdown of the repair is a rarity.

As was conclusively shown in animals by Guyer and me,<sup>1</sup> the fixation of cancerous tissues *in situ* has no tendency to increase metastasis. Similarly, the chemosurgical treatment of cancer in man has not shown evidence of causing any increase in metastasis. Neither has it been observed to cause any increase in local spread.

It must be admitted that the chemosurgical method is a time-consuming procedure requiring a certain amount of patience on the part of the operator. Moreover, it requires a special type of skill, a special knowledge of the somewhat altered microscopic appearances and a special type of equipment. For good results experience and practice are required not only on the part of the operator but on the part of his technical assistants. Hence, the method is not suitable for use in the average physician's office. It would seem necessary to limit its use to physicians who are willing to obtain the special training required and to devote considerable attention to this field. Close cooperation between specialists in surgery, radiation therapy, chemosurgery, pathology and the other specialties dealing with the treatment of cancer in a general hospital is desirable.

In order to avoid the unthinking criticism that the chemosurgical method described here is "just another escharotic" and also to prevent this work from stimulating the use of the so-called "escharotic treatments" still in use, largely by charlatans or irregular practitioners, it should be emphasized that the most important characteristic of my method is the systematic microscopic control which it affords. Any method lacking a means for a microscopic check on the progress of removal is blind, and the outcome of the treatment of cancer by such methods will be either recurrence of the neoplasm or excessive destruction of normal tissue, or both.

#### CONCLUSIONS

The chemosurgical method for the treatment of cancer involves the chemical fixation of tissues so that they may be excised in stages and systematically studied under the microscope as a guide to treatment. The microscopic control thus obtained makes possible the extirpation of any accessible neoplasm with unprecedented reliability and with a minimum destruction of adjacent normal tissue. The method requires special training and a specially equipped clinic.

# TREATMENT OF APPENDICITIS AT FRANKFORD HOSPITAL

A THIRTY-SIX YEAR SURVEY OF 4,650 CASES

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The many papers on appendicitis which have dealt with the analysis of given series of cases have shown quite conclusively (1) that in a careful surgical service there will be only an occasional death when the pathologic process is limited to the appendix; (2) that when treatment is delayed the death rate rises rapidly, and (3) that most of the fatalities occur when the appendicitis is complicated by abscess or by general peritonitis. An analysis of 4,650 cases of appendicitis from the surgical service of the Frankford Hospital well substantiates these conclusions.

This institution is a general hospital with one hundred and forty beds for the care of the community sick, having ward and private patients. The majority of the patients are in the low income group. All patients admitted with a primary diagnosis of appendicitis for the period 1904 to 1939, inclusive, are considered in this study. Only those patients who underwent an operation primarily for appendicitis or who died from appendicitis without operation are included. Patients on whom appendectomy was performed incidentally to another operation are not included unless appendicitis was found to be the primary cause of the symptom complex. Patients not operated on are excluded; most of these were persons who presumably had acute, subsiding acute or chronic appendicitis and left the hospital against advice and alive. Twelve surgeons are responsible for most of the operations performed, the remainder being distributed among twelve casual operators and attending surgeons.

The object of this survey of mortality statistics is to determine from such data whether any useful information may be obtained as to the factors which influence the mortality from the disease. Accord-

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† Dr. Nassau died August 11.

From the Surgical Service of the Frankford Hospital.

ingly, an effort will be made to determine accurately: (1) the mortality rate in this series; (2) certain factors which have been observed to influence mortality, namely, age, sex, pregnancy and type of appendicitis; (3) the cause of each death, and (4) the ultimate responsibility of appendicitis and associated lesions for each death.

Furthermore, this study is a record of a series of cases since 1904 which have been managed by a uniform plan of procedure (with minor variations), the technic of which was instituted by one of us (Nassau). Presentation of the series, therefore, should offer an opportunity for helpful analysis and criticism. Usually when a diagnosis was made the patient was operated on. If the disease was considered acute, the patient was operated on immediately; if it was not considered acute, the time of operation was elective. If the surgeon was in doubt, most of the patients were subjected to emergency operation.

#### TECHNIC

The McBurney incision was used for men and children whenever the diagnosis was certain; the right rectus incision was used almost routinely for women. The appendix was removed in all cases except when, in the presence of perforation with abscess or peritonitis, removal would necessitate excessive trauma and concomitant spread of infection. The stump was usually electrocauterized and invaginated into the cecum by a black silk modified purse string stitch. In many cases suction was used to drain peritoneal fluid and pus. When frank pus presented the wound was left completely open, no sutures whatever being used. A dressed drain<sup>1</sup> was placed into the bottom of the pelvis. After the dressed drain was in place, plain or iodoform gauze was used to keep the wound open and the tube in place.

In uncomplicated cases the patients were given tea and tap water for the first twenty-four hours, a fluid diet the second day, an enema and a laxative the third morning (with a soft diet) and the regular house diet from the fifth day. Small doses of morphine sulfate were given for pain as needed. Vomiting due to gastric dilatation or to intestinal distention was controlled by Wangensteen suction. In cases of appendicitis complicated by peritonitis, intravenous infusion of 5 per cent dextrose and physiologic solution of sodium chloride was started at once and continued by indwelling cannula at the rate of 2,500 to 3,000 cc. in twenty-four hours until fluids were retained by mouth and the tone of the bowel was restored. Transfusions were given as indicated. Removal of the drain began about the seventh or eighth postoperative day; this was replaced by a gauze wick extending nearly to the same depth as the drainage tube originally extended. The wick was removed gradually, and the wound was freed of all drainage about the fourteenth postoperative day and sometimes earlier.

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1. Nassau, C. F.: *S. Clin. North America* 17:43, 1937.

## MORTALITY

Table 1 shows the annual mortality rate for the entire group. There were 152 deaths in 4,650 cases, a general mortality of 3.27 per cent. The death rate has decreased from 1930 until 1939, with fluctuations during the past three years, and for the last eight years the level has been below the series average of 3.27 per cent. Chart 1 shows the

TABLE 1—*Mortality Rate in Cases of All Forms of Appendicitis at the Frankford Hospital from 1904 to 1939, Inclusive*

Year	Annual Mortality Rate		Mortality, per Cent
	Number of Cases	Number of Deaths	
1904	4	0	0
1905	7	1	14.2
1906	7	0	0
1907	10	0	0
1908	43	3	7
1909	60	1	1.66
1910	86	1	1.1
1911	78	1	1.3
1912	84	1	1.2
1913	79	3	4.0
1914	71	2	2.8
1915	75	4	5.3
1916	54	3	5.5
1917	63	3	4.8
1918	41	4	9.7
1919	55	5	9
1920	92	3	3.2
1921	107	6	5.6
1922	104	5	4.8
1923	153	12	7.8
1924	130	6	4.6
1925	131	9	6.9
1926	166	2	1.2
1927	171	12	7
1928	178	2	1.1
1929	192	5	2.6
1930	249	11	4
1931	222	8	3.6
1932	246	7	2.8
1933	247	7	2.8
1934	212	7	3.3
1935	176	3	1.7
1936	230	2	0.6
1937	265	5	1.9
1938	265	2	0.75
1939	301	6	2
Total	4,650	152	3.27

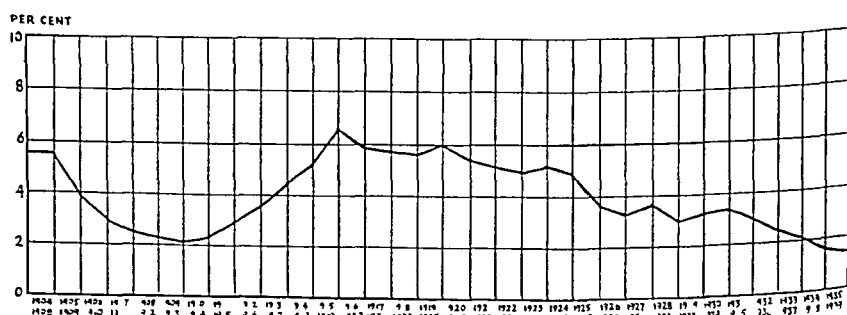


Chart 1—Progressive five year average mortality rates for all forms of appendicitis at the Frankford Hospital

progressive five-year average mortality rate for all cases. The last thirteen periods show a definite decrease. For the past two periods there has been a record low level.

Table 2 presents the mortality according to sex. The ratio of females to males was 1.3 to 1. However, the mortality among males was more than twice as great as among females. This is explained by

TABLE 2.—Incidence of Fatal Appendicitis According to Sex

Sex	Total Cases	Percentage of Total	Fatal Cases	Percentage of Total	Mortality, Percentage
Male... ..	2,010	43.1	92	60.5	4.58
Female .. . . .	2,640	56.9	60	39.5	2.27
Totals.....	4,650		152		Average 3.7

TABLE 3.—Incidence of Types of Appendicitis in Relation to Sex

Type of Appendicitis	Males		Females	
	No. of Cases	Deaths	No. of Cases	Deaths
Simple acute . . . . .	662	5	1,138	3
Chronic . . . . .	279	3	921	4
	941	8 (0.85%)	2,059	7 (0.34%)
Acute gangrenous . . . . .	738	24	421	17
Acute with perforation . . . .	249	54	107	30
Acute with abscess . . . . .	82	6	53	6
	1,069	84 (7.85%)	581	53 (9.07%)
Total.. . . .	2,010	92	2,640	60

TABLE 4.—Mortality in Age Groups (by Decades)

Age, Years	Number of Cases	Deaths	Percentage of Mortality	Percentage of Operative Mortality
0-9	296	17 (3*)	5.74	4.72
10-19	1,557	32 (7*)	2.05	1.60
20-29	1,492	18 (3*)	1.20	1.00
30-39	759	31 (2*)	4.08	3.82
40-49	334	22 (3*)	6.58	5.68
50-59	139	15 (4*)	10.79	7.91
60-69	58	11 (4*)	18.96	12.07
70-79	13	6 (1*)	46.15	38.46
80-82	2	1	50.00	50.00

\* Nonoperative cases

the fact that the incidence of complicated forms of appendicitis in the male is more than double that in the female, although in complicated cases the mortality for the two sexes is approximately the same (table 3).

In table 4 appears the distribution of cases by decades, with the number of deaths, the total mortality and the operative mortality. The youngest patient was 5 months old, with acute gangrenous appendicitis complicated by intussusception of the cecum. This patient died. The oldest was 82, with acute gangrenous appendicitis. He recovered.



The greatest incidence (81.8 per cent of all cases), and the lowest mortality (2.12 per cent average), was in the 10 to 39 year age group. The mortality in the first decade was 5.74 per cent, which compares favorably with that noted in many of the series reported (Caldwell,<sup>2</sup> 27 per cent; McLanahan,<sup>3</sup> 3.9 per cent; Beekman,<sup>4</sup> 7.6 per cent; Stone,<sup>5</sup> 7.7 per cent; Woodall,<sup>6</sup> 7.4 per cent; Tasche,<sup>7</sup> 8.5 per cent). The increased mortality among adults over 40 has been repeatedly stressed (Maes, Boyce and McFetridge<sup>8</sup>), the average being 10 per cent for 546 cases.

Twenty-six women were operated on during pregnancy, with 1 death, an operative mortality of 3.60 per cent. One woman was treated by Ochsner's method, with a fatal outcome. Twenty-five of the women had acute appendicitis, and 2 had chronic appendicitis. There were 3 miscarriages, and in 2 cases the fetus died.

TABLE 5—*Appendicitis Complicating Pregnancy*

	Number of Cases			
	Acute	Chronic	Miscarriages	Deaths *
First trimester	5	0	0	0
Second trimester	9	1	1	1
Third trimester	8	0	1	1
No record of duration of pregnancy	3	1	1	0
Totals	25	2	3	2

\* One of the 2 patients who died was a white woman aged 32 who had had symptoms for six days. This patient was in the seventh month of pregnancy when she had pain in the right lower quadrant of the abdomen. She fell into labor and was delivered of a living premature baby. The pain continued. Seven days after delivery she was transferred to the surgical service. By this time the condition was critical. She was not operated on. She died within twenty-four hours. The other was a white woman aged 39 who had had symptoms for about forty-eight hours. She was five months pregnant. The diagnosis was acute gangrenous appendicitis with generalized peritonitis, gangrene of the ileum and thrombosis of the mesenteric vessels. Appendectomy, drainage and ileostomy were performed three hours after admission. After the third postoperative day the course was stormy. On the twelfth day she was delivered of a five-month fetus, which was not viable. She died ten hours later, of generalized peritonitis.

Since 1910 all of the patients in this series have been studied histopathologically. When there has been disagreement between the pathologist's report and the clinical diagnosis, the pathologist's diagnosis has been assumed to be correct.

*Pathologic Classifications.*—There are 5 types:

1. Acute Catarrhal Appendicitis: This is an acute inflammatory process confined to the mucous membrane and the deeper structures of the appendix.

2. Caldwell, E. H.: Surg., Gynec. & Obst. **67**:169, 1938

3. McLanahan, S.: Am J. Surg. **25**:14, 1934

4. Beekman, F.: Ann Surg. **79**:538, 1924.

5. Stone, C. S., Jr.: Acute Appendicitis in Children, Arch Surg **30**:346 (Feb.) 1935.

6. Woodall, C. W.: New York State J. Med. **28**:322, 1928

7. Tasche, L. W.: Am J. M. Sc. **182**:86, 1930.

8. Maes, U.; Boyce, F., and McFetridge, E. M.: Am J. Surg **23**:157, 1934

2. Acute Gangrenous Appendicitis: This includes the suppurative type. The acute inflammatory process is not limited to the appendix. The peritoneum is affected in varying degrees. Free nonpurulent fluid is present in the abdominal cavity.

3. Acute Appendicitis with Perforation: There are varying degrees of associated peritonitis. No attempt has been made to classify the peritonitis as local or spreading.

4. Acute Appendicitis with Perforation and Abscess Formation: This corresponds with the condition just described except for the additional complication by abscess.

5. Chronic Appendicitis: This includes appendical fibrosis, obliterative appendicitis and catarrhal appendicitis without evidence of acute inflammation.

Obviously this classification is for the purpose of convenience. It was made in order that the treatment might be evaluated, and also to

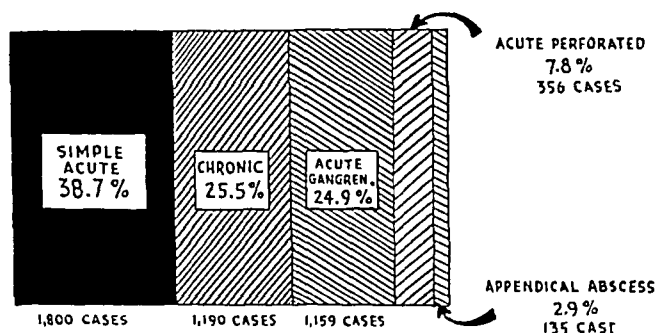


Chart 2.—Data on 4,650 cases of appendicitis observed at the Frankford Hospital from 1904 to 1939.

ascertain whether the mortality can be reduced. Prior to 1910 there were many cases in which it was extremely difficult to determine the exact category, the meagerness of the early records creating a definite handicap in this connection. Thus, in many cases acute appendicitis with gangrene and general peritonitis might be more properly classified under acute appendicitis with perforation. This is the likely explanation for the high mortality from acute gangrenous appendicitis in the early years.

The distribution of the different conditions is illustrated in chart 2. In 64.2 per cent (2,990) of all the cases there was uncomplicated appendicitis, whereas in 35.8 per cent (1,660) there were advanced stages of the disease. If chronic appendicitis is not included and the acute appendical conditions only are considered, then 47.9 per cent (12 of every 25) of the patients who came to operation already had a serious form of appendicitis (gangrenous, perforative or accompanied with abscess).

In 14.2 per cent of the cases of acute involvement (1 of every 7 cases) the condition had already progressed to the point of rupture, with either spreading peritonitis or abscess formation.

In table 6 the five classes of appendicitis are set out, with the number of cases, the number of deaths and the mortality rate. Charts 3, 4, 5 and 6 give the facts concerning the progressive five year average mortality rates for the acute conditions.

TABLE 6.—*Annual Mortality Rates in Cases of Acute and Chronic Appendicitis at the Frankford Hospital, 1904 to 1939, Inclusive*

Year	Simple Acute			Acute Gangrenous			Appendical Abscess			Acute with Perforation			Chronic		
	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent	Number of Cases	Number of Deaths	Mortality, per Cent
1904	3	0	0	0	0	0	1	0	0	0	0	0	0	0	0
1905	4	0	0	0	0	0	2	0	0	1	1	100	0	0	0
1906	6	0	0	0	0	0	0	0	0	0	0	0	1	0	0
1907	5	0	0	0	0	0	2	0	0	0	0	0	2	0	0
1908	26	0	0	6	2	33.3	4	1	25	0	0	0	7	0	0
1909	48	0	0	2	0	0	0	0	0	2	1	50	6	0	0
1910	72	0	0	6	1	16.6	3	0	0	4	0	0	1	0	0
1911	56	0	0	5	0	0	5	0	0	2	1	50	10	0	0
1912	40	0	0	10	0	0	8	0	0	5	1	20	21	0	0
1913	39	0	0	17	2	11.8	2	0	0	2	1	50	16	0	0
1914	27	0	0	15	1	6.6	6	0	0	1	1	100	22	0	0
1915	28	0	0	17	2	11.8	6	1	16.6	2	0	0	23	1	4.4
1916	25	0	0	8	0	0	0	0	0	12	3	25	9	0	0
1917	28	0	0	6	0	0	3	0	0	9	3	33.3	17	0	0
1918	14	1	7.1	9	3	33.3	1	0	0	4	0	0	13	0	0
1919	23	0	0	11	2	18.1	1	0	0	10	3	30	10	0	0
1920	33	0	0	21	1	4.7	4	1	25	7	1	14.2	27	0	0
1921	46	0	0	22	1	4.5	8	1	12.5	10	3	30	20	1	5
1922	42	0	0	25	1	4	2	1	50	14	3	21.4	21	0	0
1923	52	1	1.9	34	4	11.7	6	0	0	18	7	38.9	43	0	0
1924	32	0	0	33	1	3.3	5	0	0	13	4	30.7	47	1	2.1
1925	38	1	2.6	40	2	5	8	2	25	11	4	36.3	34	0	0
1926	31	1	3.1	68	1	1.5	1	0	0	9	1	11.1	55	0	0
1927	32	0	0	52	3	5.7	5	1	20	17	5	29.4	65	2	3.1
1928	66	0	0	45	0	0	5	0	0	3	2	66.6	59	0	0
1929	81	1	1.2	57	2	3.5	3	0	0	9	2	22.1	41	0	0
1930	121	1	0.82	66	6	9	5	0	0	18	4	22.2	39	0	0
1931	102	1	0.97	40	2	5	7	0	0	22	5	22.7	51	0	0
1932	91	0	0	54	0	0	4	0	0	31	7	22.5	65	0	0
1933	95	0	0	74	1	1.3	4	2	50	17	3	17.6	57	1	1.75
1934	61	0	0	78	3	3.8	6	0	0	10	3	30	56	1	1.77
1935	53	0	0	60	0	0	3	1	33.3	9	2	22.2	45	0	0
1936	70	0	0	62	0	0	5	0	0	18	2	11.1	75	0	0
1937	78	0	0	81	0	0	3	0	0	21	5	23.7	80	0	0
1938	99	0	0	66	0	0	4	1	25	22	1	4.5	74	0	0
1939	129	1	0.77	69	0	0	2	0	0	23	5	21.7	78	0	0
Total, 1,800	8			1,159	41		135	12		356	84		1,190	7	
Average			0.44			3.5			8.8			23.6			0.59

*Simple Acute Appendicitis and Chronic Appendicitis.*—The operative mortality for these two conditions was 0.44 per cent and 0.59 per cent respectively—virtually nil. As will be shown later, the deaths from these processes were such as might occur in any large series of operations. The best results in cases of appendicitis, then, are obtained when the patient is seen early and operation is done early. The convalescence is rapid, and the patient's health is restored without much loss of time.

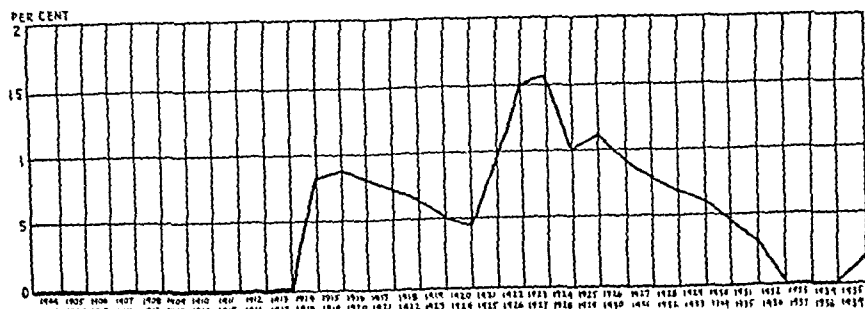


Chart 3.—Progressive five year average mortality rates in cases of simple acute appendicitis at the Frankford Hospital.

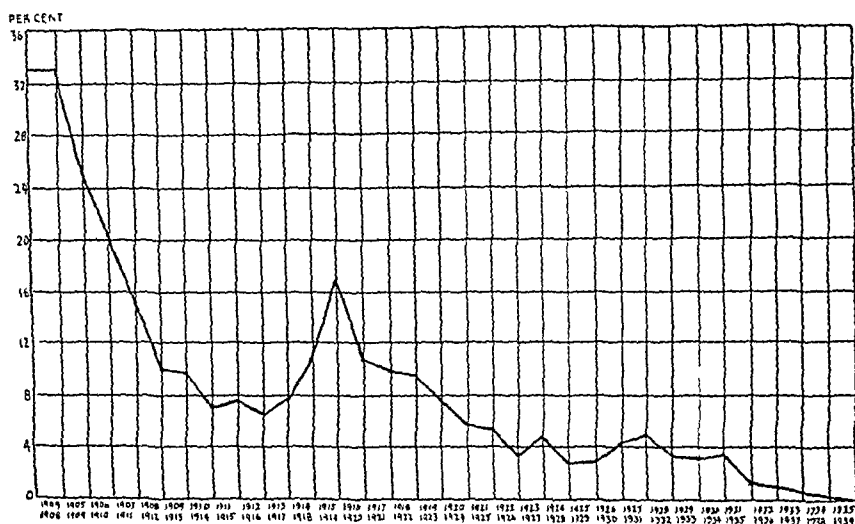


Chart 4.—Progressive five year average mortality rates in cases of acute gangrenous appendicitis at the Frankford Hospital.

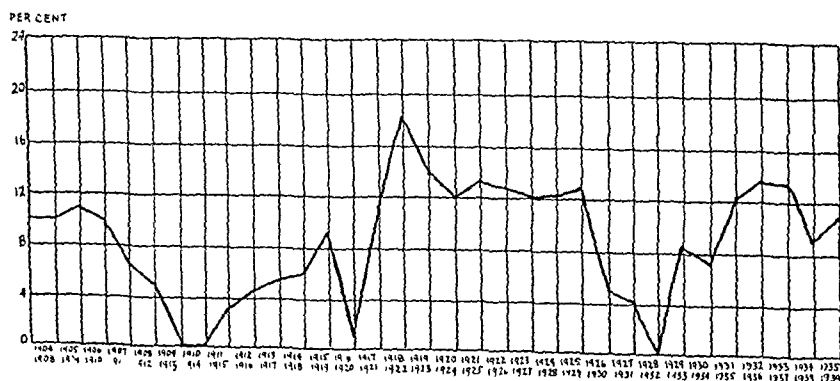


Chart 5.—Progressive five year average mortality rates in cases of appendical abscess at the Frankford Hospital.

*Acute Appendicitis with Gangrene.*—This condition has been most difficult to classify. Numerous discrepancies were found between the surgeon's description of the operative findings and the final notes. Many of the conditions recorded under this heading might have been placed elsewhere, especially under perforation. The early records particularly are difficult to evaluate, because of their meagerness. The suppurative or rapidly fulminating conditions are included under the one heading. No attempt has been made to denote the degree of peritonitis present. However, the pathologic classification is accurate and eliminates the variable personal factor, and for this reason it has been adopted. One pathologist has examined nearly all the tissues throughout the period of this study.

The patients with general peritonitis in this class were drained. When the peritonitis tended to localize, the wound was closed at operation. Many wounds today are closed which would formerly have been drained.

In examining chart 4 one is impressed by a distinct drop in the mortality rate. There are a few rises, the greatest in the period from 1914 to 1922. This may be explained in part by the fact that when the regular attending surgeons were drafted into the World War they were replaced by surgeons with less operative experience. The mortality rate of acute gangrenous appendicitis is definitely decreasing. The average mortality rate for this condition is 3.5 per cent. However, during the past five years there have been no deaths in 338 cases.

*Appendical Abscess.*—There were 135 cases of abscess. Twelve of the patients died, an average mortality of 8.8 per cent. Three of the 12 deaths occurred in cases in which operation was delayed in the hope of localization. However, the patients died of septicemia before operation was done. Blood cultures were not recorded. This leaves an operative mortality of 6.6 per cent. The higher mortality is in contrast to that in the three groups discussed previously. While the number of cases is not increasing, chart 5 shows an increasing mortality rate since the period from 1928 to 1932, and since that period the rate has been well above the average of 8.8 per cent. One of the principal factors which enter into the treatment of this condition is drainage—when to drain and how to drain. When it is apparent that infection is spreading and general peritonitis is imminent, operation ought not to be delayed. On the other hand, when the abscess is localizing and the patient's condition indicates recovery, operation may be withheld until the abscess is well walled off. The limits of delay must be decided by the progress of the disease. When operation is performed, what is to be done can be decided only at the time of operation. When localization occurs in the pelvis, incision and drainage by rectum have

been our practice. When the peritoneal cavity is opened, in addition to drainage, the appendix is removed only when no additional trauma will be provoked.

*Acute Appendicitis with Perforation and Peritonitis.*—The mortality in this group was 23.6 per cent in 356 cases and represents 55.3 per cent of all the deaths in the series. Twenty-one of the deaths occurred in cases in which operation was not done, leaving 63 deaths, an operative mortality of 17.6 per cent. This figure is not unfavorable when compared with those reported from other hospitals (Davis and others,<sup>9</sup> 25.5 per cent; Finney,<sup>10</sup> 21 per cent; Kirtley and Daniel,<sup>11</sup> 16.3 per cent; Pattison,<sup>12</sup> 28.7 per cent; Totten,<sup>13</sup> 26 per cent; Schullinger,<sup>14</sup> 17.02 per cent).

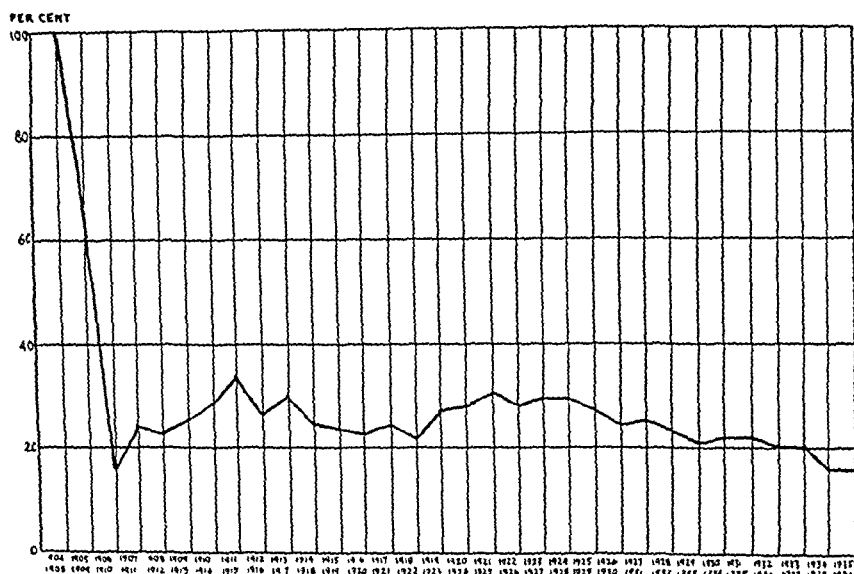


Chart 6.—Progressive five year average mortality rates in cases of acute perforative appendicitis with peritonitis at the Frankford Hospital.

Chart 6 shows a remarkable constancy in the mortality rate in this group. The last two periods show the lowest rates on record, 7.4 per cent below the average mortality of 23.6 per cent.

9. Davis, J. E.; Muske, P. H.; Mulligan, P. L., and Gutov, J.: *Appendicitis: Statistical Survey of Ten Thousand Cases at Providence Hospital*, J. A. M. A. **108**:1498 (May 1) 1937.

10. Finney, J. M. T., Jr.: *Surg., Gynec. & Obst.* **56**:360, 1933.

11. Kirtley, J. A., and Daniel, R. A.: *Surgery* **2**:215, 1937.

12. Pattison, A. C.: *Ann. Surg.* **103**:362, 1936.

13. Totten, H. P.: *Ann. Surg.* **106**:1035, 1937.

14. Schullinger, R. N.: *Acute Appendicitis and Associated Lesions: Some Observations on Mortality*, *Arch. Surg.* **32**:65 (Jan.) 1936.

*Total Mortality Rate.*—In table 7 and chart 7 is presented the total mortality rate for all cases of acute appendicitis. There has been a decline in the mortality since the period from 1924 to 1928, and the

TABLE 7.—*Mortality Rate in Cases of All Forms of Acute Appendicitis at the Frankford Hospital from 1904 to 1939, Inclusive*

Year	Annual Mortality Rate		Mortality, per Cent
	Number of Cases	Number of Deaths	
1904	4	0	0
1905	7	1	14.2
1906	6	0	0
1907	8	0	0
1908	35	3	8.5
1909	53	1	1.9
1910	84	1	1.1
1911	67	1	1.5
1912	62	1	1.6
1913	58	3	5.1
1914	49	2	4.1
1915	53	3	5.6
1916	45	3	6.6
1917	46	3	6.5
1918	28	4	14.3
1919	45	5	11.1
1920	65	3	4.6
1921	87	5	5.7
1922	83	5	6
1923	110	12	9.1
1924	83	5	6
1925	97	9	9.2
1926	110	2	1.8
1927	106	10	9.4
1928	119	2	1.7
1929	151	5	3.3
1930	210	11	5.2
1931	171	8	4.7
1932	180	7	4.4
1933	190	6	3.1
1934	155	6	3.9
1935	131	3	2.3
1936	155	2	1.3
1937	184	5	2.7
1938	191	2	1.05
1939	223	6	2.7
Total	3,451	145	4.2



Chart 7.—Progressive five year average mortality rates for all forms of acute appendicitis at the Frankford Hospital.

rate has been below the 4.2 per cent average mortality for the last five periods. There were 28 deaths in nonoperative cases in this group, which if excluded would reduce the mortality to 3.38 per cent. This figure is

low as compared with many given when large series of cases have been reported (Black,<sup>15</sup> 4.1 per cent; Bower,<sup>16</sup> 4.79 per cent; Finney,<sup>10</sup> 2.33 per cent; Garlock,<sup>17</sup> 4.7 per cent; Keyes,<sup>18</sup> 5 per cent; Quain,<sup>19</sup> 3.2 per cent; Reid and his associates,<sup>19a</sup> 6.3 per cent; Schullinger,<sup>14</sup> 4.51 per cent; Sprague and others,<sup>20</sup> 2.73 per cent). The total mortality rate for the entire group, cases of chronic appendicitis included, has already been presented (table 1).

*Analysis of Deaths.*—In table 8 are listed the causes of death. Generalized peritonitis heads the list, and at the time of operation it had already been present in 89 of the 152 patients who died. Of these, 12 were moribund when operated on, and they died within twenty-four

TABLE 8.—Causes of 152 Deaths in 4,650 Cases of Appendicitis

	Total Number of Cases	Per Cent of Total	Simple Acute	Acute Gan- gren- ous	Acute with Abscess	Acute with Perfo- ration	Chronic
General peritonitis.....	91	59.8	0	23	8	59	1
General peritonitis plus pulmonary abscess...	1	0.65	..	..	..	1	..
Intestinal obstruction.....	19	12.5	3	8	1	7*	..
Myocardial insufficiency.....	15	9.8	1	2	2	8*	2
Pneumonia.....	9	5.9	2	2	..	5*	..
Embolie phenomena:							
Pulmonary embolism.....	1	0.65	..	..	..	..	1
Cerebral embolism.....	2	1.3	..	1	..	..	1
Mesenteric thrombosis.....	3	1.9	..	1	..	1*	1
Fecal fistula.....	3	1.9	1	2	..	..	..
Diabetes.....	3	1.9	..	1	1	1*	..
Nephritis.....	4	2.5	..	1	..	2*	1
Diverticulitis (Meckel's diverticulum).....	1	0.65	1	..	..	..	..
Gangrene of omentum in incarcerated hernia	1	0.65	1	..	..	..	..
Totals.....	152		8	41	12	84	7

\* With complicating general peritonitis.

hours. For 26 more operation was delayed, and they died of generalized peritonitis without benefit of operation. In 116 of the fatal cases (3 of every 4), then, generalized peritonitis was a primary cause of death. Intestinal obstruction was responsible for 19 deaths; in 7 cases it was accompanied with generalized peritonitis. Myocardial insuffi-

15. Black, C. E.: Bull. Am. Coll. Surgeons **16**:22, 1932.

16. Bower, J. O.: Acute Appendicitis in Philadelphia: Report of Progress Made in Campaign for Its Reduction, J. A. M. A. **102**:813 (March 17) 1934.

17. Garlock, J. H.: Am. J. Surg. **23**:248, 1934.

18. Keyes, E. L.: Ann. Surg. **99**:47, 1934.

19. Quain, E. P.: Acute Appendicitis: Second Report of One Thousand Consecutive Cases, Arch. Surg. **28**:782 (April) 1934.

19a. Reid, M. R.; Poer, D. H., and Merrell, P.: A Statistical Study of 2,921 Cases of Appendicitis, J. A. M. A. **106**:665 (Feb. 29) 1936.

20. Sprague, E. W., and others: Surg., Gynec. & Obst. **66**:166, 1938.



ciency cost 15 lives, embolic phenomena 6 and pneumonia 9. Three patients died after complications from fecal fistula, 3 from diabetes and 4 with nephritis and uremia. One died as the result of diverticulitis of a Meckel diverticulum and 1 from gangrene of the omentum in an incarcerated hernia. It is possible that in these 2 patients the appendix was simply congested by reason of its inclusion in the attendant pathologic process instead of being primarily inflamed, and there is some doubt as to the actual cause of death.

The 7 deaths from attendant medical diseases might have been prevented. The number of victims of vascular accidents might be decreased by selecting with extreme care for elective operations patients who have a narrow cardiovascular reserve. Five of the patients in these fatal cases were operated on for chronic appendicitis and a sixth for simple acute appendicitis. Great care should be given the choice of an anesthetic in the presence of heart disease. At present the use of spinal or local anesthesia seems highly desirable.

Likewise, general anesthesia ought to be avoided in the presence of infection of the upper respiratory tract. Turning the patient from side to side and encouragement of deep breathing soon after the operation are good prophylactic measures.

As regards patients with generalized peritonitis, the treatment requires careful judgment. Proper choice of an anesthetic is important; spinal or local anesthesia should be preferred. As little trauma as possible should be attendant on the operation, and the appendix should not be removed when spread of infection will follow. Drainage and postoperative care have already been discussed. However, it cannot be too much emphasized that rest and large amounts of fluids are very important and that Wangenstein suction is of great value in the prevention of gastric dilatation and distention. Distention and paralytic ileus are extremely difficult to handle. The Miller-Abbott tube<sup>20a</sup> and pitressin and prostigmine methylsulfate<sup>20a</sup> have recently been reported<sup>21</sup> to be of value if used both preoperatively and postoperatively. However, it may be that the greatest advance in the treatment of generalized peritonitis is the use of parenteral sulfanilamide as reported by Ravdin and his co-workers.<sup>22</sup> In his report Ravdin recorded only 1 death in 252 cases, a remarkable record. Many cases will have to be observed to bear out these results.

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20a. Whipple, A. O.: *The Use of the Miller-Abbott Tube in the Surgery of the Large Bowel*, *Surgery* 8:289 (Aug.) 1940.

21. Marden, P. A., and Williamson, E. G.: *Surg., Gynec. & Obst.* 69:61, 1939.

22. Ravdin, I. S.; Rhoades, J. D., and Lockwood, J. S.: *Ann. Surg.* 111:53, 1940.

## COMMENT AND SUMMARY

In a recent editorial in the *Journal of the American Medical Association*<sup>23</sup> entitled "The Challenge of Appendicitis" it is stated: "The mortality from acute appendicitis has risen sharply during the past few decades," and this evidently in spite of advances in treatment. The cases of 4,650 patients admitted to the Frankford Hospital between 1904 and 1939 inclusive have been analyzed, and a general decline of the mortality rate has been noted. There is some suggestion that there is a real increase in the incidence, yet the case fatality has fallen considerably. The decrease in mortality must be real, as differentiation of the available data shows a drop in the mortality rate for all conditions except appendical abscess, in which some increase has been noted. The total mortality rate from all forms of appendicitis in this series was 3.27 per cent, and from acute appendicitis, 4.2 per cent. The total death rate for the five divisions was as follows: simple acute appendicitis, 0.44 per cent; chronic appendicitis, 0.59 per cent; acute appendicitis with gangrene, 3.5 per cent; appendical abscess, 8.8 per cent, and acute appendicitis with perforation and peritonitis, 23.6 per cent. The curves of the progressive five year average mortality rates show an appreciable decline for all conditions except appendical abscess. The increase in mortality in the period from 1915 to 1922 may have been due to change to a less experienced personnel.

The McBurney incision is preferred by us for men and children and the right rectus incision for women. The usual practice is to operate at once and to remove the appendix in all cases if possible. It is the custom to drain all patients with spreading peritonitis.

There were more females than male patients, apparently owing to the large number of cases of chronic appendicitis in which women were operated on. The more severe forms of appendicitis occurred in males, and, concomitantly, the mortality rate was higher for men. The mortality rate in pregnancy was 3.60 per cent for 26 cases.

The highest incidence and the lowest mortality rate were in the 10 to 39 year age group. Below the age of 10 years and above that of 40 the mortality rate increased.

Accompanying medical disease exerts a profound influence on the prognosis of appendicitis. Cardiovascular disease, pneumonia and nephritis were major causes of death, and some of these might have been prevented. However, appendicitis causes most of the deaths. In 116 of the 152 fatal cases in this series peritonitis was the primary cause of death. In 28 of these cases death followed delay of operation in an effort to localize spreading peritonitis.

23. The Challenge of Appendicitis, editorial, J. A. M. A. **112**:2066 (May 20) 1939.

As is well known, the mortality of any disease can be lowered by reducing its incidence and by improving methods of diagnosis and treatment. Too little is still known about predisposing factors to enable physicians to devise effective methods of prevention of appendicitis. Therefore, one must concern oneself almost entirely with improving methods of diagnosis and treatment. As regards diagnosis, typical appendicitis is easy to recognize, and the results from operative intervention after prompt recognition are good. The atypical condition, however, is met not infrequently, and the physician may not recognize the disease, especially if it is early. In case of doubt, one should not give opiates and wait until the next day to see the patient again; rather, the patient should be observed frequently until more definite signs develop, and, if there is continued doubt, consultation with an older and more experienced physician should be requested. The general practitioner should learn to regard with suspicion any abdominal pain lasting over six hours and should not loiter before referring the patient to the surgeon. As regards treatment, this is entirely surgical, and the earlier it is instituted the fewer the complications. The deaths in cases of appendicitis being nearly all from peritonitis, the hope of influencing future mortality statistics lies in the prevention and improved management of peritonitis. Continued education of the public as to the indiscriminate use of cathartics for abdominal pain and the seriousness of delay is essential. It should be stressed that the pain of appendicitis begins in the upper part of the abdomen and around the umbilicus rather than in the right lower quadrant. The economic factor should make a strong appeal to the public. The average patient whose condition is uncomplicated leaves the hospital in nine to ten days, whereas for patients with appendicitis complicated by peritonitis the stay may be doubled or trebled, with some degree of residual disability.

Our treatment of peritonitis is presented and the meticulous manner of drainage emphasized. The recording of this series of cases is of value in that it shows results of following a uniform technic in the management of peritonitis. The use of sulfanilamide and allied drugs in the prevention and treatment of peritonitis offers great promise for the reduction of mortality from this dreaded complication.

## APPENDIX VERMIFORMIS DUPLEX

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MONTREAL, CANADA

The appendix is such a common surgical specimen that one hardly anticipates the possibility of its duplication. However, although it is a very rare anomaly, the so-called double appendix does occur, and it offers a number of interesting points for consideration.

The first question which naturally arises is: What is an appendix, and what are the criteria by which one may identify the organ and separate it from other types of protrusions from the cecum? Cave, in an extensive summary of the knowledge of the comparative anatomy of this region, concluded, contrary to common belief, that a true vermiform appendix identical to that met with in man is found only in gibbons and anthropoid apes, although, peculiarly enough, monotremes and some marsupials possess a strikingly similar structure. Aside from its gross form and position, histologically the appendix is identified and distinguished from the cecum by the amount and arrangement of its lymphoid tissue and by the presence of both an inner circular and an outer longitudinal muscular coat.

Secondly, in contrast to many anomalous duplications in the human body for which one has a clear and accepted embryologic explanation, there has never been any uniformity of opinion about the mechanism by which the double appendix occurs. Several hypotheses have been advanced by different authors. This is probably due principally, as will be shown later, to the fact that there are at least four distinct types of this condition, which are so essentially different that it seems reasonable to assume that each arises as the result of an independent form of developmental disturbance. These will be taken up under the review of cases found in the literature.

Furthermore, there is the practical side of the problem, which particularly concerns the general surgeon, since this anomaly involves his most commonly frequented field. There are a number of occasions on record in which the appendix was removed or at least was reported to have been removed, in which the patient's abdomen was again opened for one reason or another and an appendectomy performed. Under such circumstances one is naturally hesitant about accepting the duplicity of the appendix as positively established. However, when both operations

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have been performed by the same surgeon or satisfactory pathologic records of the excised tissues are obtainable, one is by no means justified in dismissing the evidence as beyond the bounds of credence. Fortunately, cases of duplicity are sufficiently rare that even the most thorough surgeon need hardly feel compelled to explore carefully every cecum after removal of an appendix to satisfy himself that a second has not been left.

Finally, that there may be even a medicolegal aspect of the question as to whether two appendixes can occur in the same person has been demonstrated in a recent case, in which suit for damages was threatened against a surgeon on the grounds that he informed the patient, who was subsequently appendectomized, that he had removed the organ at a previous operation. Under such circumstances the pathologic examination and the record of even a normal appendix reach considerable importance.

In addition to the example to be described in detail, I have succeeded in collecting 14 cases of this anomaly from the literature. Moreover, there are included in the bibliography several references to articles touching on the subject. I have purposely omitted from this series one type of double appendix, that is, the type in which duplication of the cecum as a whole has taken place, with an appendix on each part. Greig in 1934 reported an example of this type, in which there occurred doubling of the whole bowel distal to the site of Meckel's diverticulum, and Cave in 1936 described a specimen from the teratologic series of the Hunterian Museum of the Royal College of Surgeons of England in which duplicity of the parts derived from the apex of the primitive midgut loop had occurred. Although there exists no satisfactory explanation of this embryologic phenomenon, the development of an appendix on each of the two separate cecums would occur in the usual manner as a natural course of events.

If one analyzes the 15 cases it is obvious at once that they fall into three distinct groups. Moreover, these groups are so sharply separated that, although they are all examples of duplication of the organ, one cannot but feel that they arise on quite different developmental grounds and should be considered distinct entities. The first of these consists of various types of the so-called "double-barreled" appendix. There were 5 in this series. However, as nearly every pathologist who examines a large amount of surgical material can recall having encountered at least 1 example of this curious condition, the lesion is probably by no means as rare as the scanty literature might indicate. In this type the two appendixes come off from the cecum at the normal site and comparatively close together. Their lumens may unite in a single tip, and they may be enclosed by a common muscular coat. In the examples

reported by Rosenberger (1903) and by Prentis (1907), actual doubling of the appendix did not occur. The two lumens were merely separated by the fibrous connective tissue of the submucosa, and both were invested by common muscular coats and serosa. In Walthard's case (1931) an infant's appendix was found to arise normally from a single point of the cecum. It then formed two parallel tubes 25 mm. in length, which reunited distally to form the normal single lumen of the last 10 mm. of the process. Each branch had a separate mucosa, submucosa and circular musculature, but there was a common longitudinal muscular coat and serosa, with one mesentery. Somewhat greater separation occurred in the double appendix reported by Clavel and Colson (1933). In operating on a woman 30 years of age they encountered two appendixes arising in the usual site, about 1 cm. apart. They were approximately the same length and ran parallel, confined in one serosal covering and supplied by a single artery. Toward the tip at one point there was a slight fusion, so that only the mucosae intervened between the two lumens. Otherwise, however, they were distinct. In Elwyn's (1924) case, curiously enough, there was even wider separation at the points of origin but complete fusion into a common lumen at the tip. It is interesting that in these examples of duplication there was considerable variation in the structural relation of the two parts and at the same time some degree of fusion in each.

As regards the explanation of this form of anomaly, it has been pointed out that the anlage of the cecoappendix lies partly on one side and partly on the other side of the most distal part of the umbilical loop of the entodermal tube. Such a division lends itself readily to duplication provided, as Kermauner suggested, some developing cloacal elements interfere with proper subsequent union and fusion. However, in all of these cases it is to be noted that separation is never complete. This would suggest that the disturbance in development is well localized to a comparatively small area and is probably fundamentally different from that which brings about the other types of duplication to be considered in this paper. When fusion is only slight, as in the case reported by Clavel and Colson, the question might arise whether the appendixes were originally completely separated and subsequently fused. This seems doubtful, particularly in view of the fact that it would explain only the most extreme examples of an apparently related series.

The second group of cases comprises those which might be referred to as cases of the "bird type" of duplication. There were 3 examples of this form in the series collected. The patients were all newborn infants who were the subjects of profound developmental disturbance and multiple anomalies. They were characterized by the presence of two appendixes, symmetrically placed, one on either side of the ileocecal valve. Emrys-Roberts and Paterson (1906) casually reported such a

condition in their detailed description of a stillborn full term fetus which exhibited ectopia of the viscera, spina bifida and many other abnormalities. The second case of this type was described by Pratt (1933), and Del Plaine (1936) has added a third. In this last case there were a defect in the anterior abdominal wall, agenesis of the bladder, a double uterus and a double vagina. Moreover, it was noted that each appendix revealed the typical infantile structure met with in the normal organ at this age.

The striking similarity of the arrangement to the cecums met with in birds has raised the question whether the anomaly may not represent the preservation of an ancestral form. However, it has been pointed out that the bird is a distant relative, not an ancestor, of man, and it seems more likely that some unknown force acting in early embryonic life leads to an alteration of development which subsequently proceeds along the general plan met with in the avian cecum.

There are 7 examples of the third type of double appendix, including the present case, in the series which I have collected. In each of these cases one of the appendixes came off the cecum at the usual site, where the taeniae coli come together, while the other appendix, which was inclined to be smaller and even rudimentary, was distinctly separate and arose from the cecum apparently almost invariably along the lines of one of the taeniae, a greater or lesser distance from the first. This might be referred to, therefore, as the "taenia coli" type.

The first duplication of this type to appear in the literature was described by Schooler in 1907. He reported that during the course of an appendectomy on a woman 23 years of age he found a swollen, gangrenous appendix at the usual site, while 1 inch (2.5 cm.) higher and apparently arising along the anterior taenial band, was another appendix, 4 inches (10 cm.) in length and of slightly smaller diameter, which was not inflamed. Soon afterward (1911), Young reported an operation at which two appendixes were found. One contained pus, and the other was gangrenous and ruptured. Their bases were  $1\frac{1}{4}$  inches (3.1 cm.) apart, and they measured 3 and  $3\frac{1}{2}$  inches (7.6 and 8.8 cm.) in length respectively, with separate mesoappendixes. Bérard and Vignard (1914) in their monograph on appendicitis stated that Jalaquier had observed a case of double appendix. One appendix was short and was removed at the first operation, while the second was found by chance during the course of a subsequent operation for ventral hernia. Further details are lacking. Berthold in 1932 reported finding two appendixes in a 60 year old woman who was operated on for intestinal obstruction. The cecum showed one, 7 cm. long, at the normal site; the other, 5 cm. in length, sprang 2 to 3 cm. laterally from the first, out of a haustrum coli. Histologically the former was somewhat thickened; the latter revealed

deposition of submucosal fat. Both possessed only a small amount of lymphoid tissue but sufficient, according to the views of the author, to identify them as appendixes.

Cave (1936), in an excellent review of the whole subject, described a specimen obtained by Mr. H. C. Wilson, Prosector of the Hunterian Museum of the Royal College of Surgeons of England in an otherwise unremarkable full term fetus. The cecum was of infantile type and was conical. From the left side of the apex an appendix 15 mm. in length extended inferomedially. A second appendix, which was 20 mm. long, in retrocecal position and supplied with a short mesentery, arose from the posteromedial wall of the cecum, along the line of a taenia coli, 15 mm. from the first. Its lumen opened into the cavity of the cecum. Both appendixes showed normal histologic structure. The author's explanation for this anomaly will be discussed later. The most recent contribution to this subject was made by Robertson (1940), who described an example reported to him by Boulanger from the Edmonton General Hospital. In operating on a boy for appendicitis the surgeon encountered a long retrocecal appendix having its tip under the hepatic flexure and a second appendix arising from the wall of the cecum 2 inches (5 cm.) lateral to the site of the first. The former was ruptured when removed, and the latter was slightly inflamed. Both communicated with the lumen of the cecum.

My case is that of a youth 19 years of age, who entered the Homeopathic Hospital in the service of Dr. J. J. Ostapovitch with the typical symptoms of acute appendicitis. His previous history was irrelevant. The surgeon's report, dictated immediately after the operation, was as follows:

A right lower lateral incision was made. When the abdomen was opened there was no free fluid in the peritoneal cavity. A mass was found in the right lower quadrant. The omentum was wrapped around the appendix. I could feel the appendix as it entered this mass, and I attempted to free the mass and deliver the appendix into the wound. While I was doing this some pus escaped from the mass, and this was swabbed out and prevented from entering the peritoneal cavity. As I was removing the upper and lateral part of the mass it broke off the ascending colon and cecum, and a mass of tissue about 2 cm. long, which appeared to be the stump of the appendix, was found to be protruding from the lateral side of the upper part of the cecum. I thought that this was the stump of the appendix and removed it, cauterizing the base and performing invagination with a silk suture. I then proceeded to remove the gangrenous mass, wrapped with omentum. I found that the appendix entered this mass and was attached below to the bottom of the cecum. I freed the appendix, removed it with the cautery and invaginated the stump. I also removed the gangrenous portion of the omentum which had been wrapped around the appendix. I concluded that I had made an error in thinking that the first small portion of tissue had been the stump and thought that it probably was only a piece of fat. The wound was closed in three layers. No drainage was provided for.



The specimen was received at the laboratory, and, unfortunately, routine sections were cut for histologic examination without photographing the gross material, as it was naturally believed that two appendixes from different patients had carelessly been placed in the same container. The pathologic report on the material was as follows:

*Macroscopic Examination.*—1. The specimen consisted of an appendix approximately 10 cm. long. It was swollen, thickened, somewhat dilated in the distal portion and covered with a purulent fibrinous exudate; there was also a con-

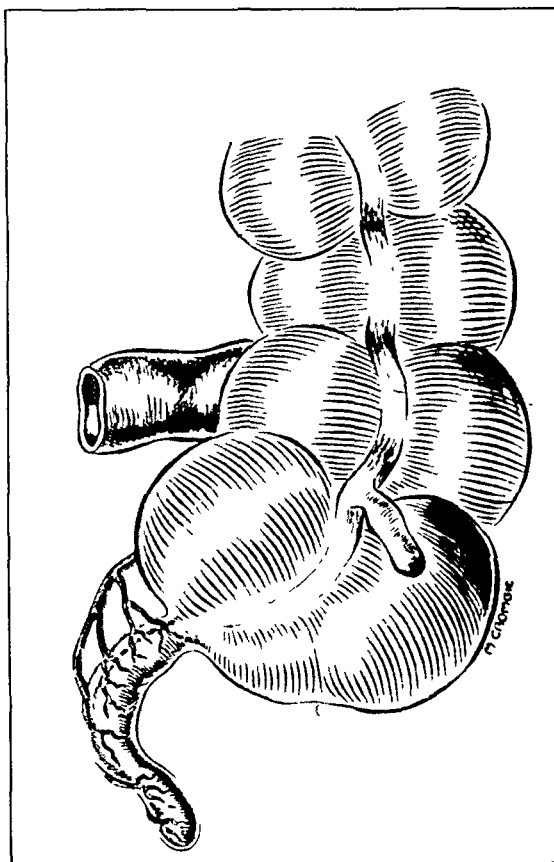


Fig. 1.—Posterolateral view, showing the relative position and size of the two appendixes.

siderable quantity of fat, one portion of which was firm and hemorrhagic. 2. In the same container there was another appendix, approximately 2 cm. in length, the wall of which was somewhat thickened. The lumen contained hemorrhagic material. The serosa was smooth and glistening.

*Microscopic Examination.*—Sections of the first appendix showed all the coats infiltrated by a purulent exudate. The wall was very hemorrhagic, and there had been an extension of the inflammatory process into the neighboring fatty tissue.

*Diagnosis.*—The diagnosis was exudative, purulent hemorrhagic appendicitis and periappendicitis.

Sections of the other appendix showed normal histologic structure.

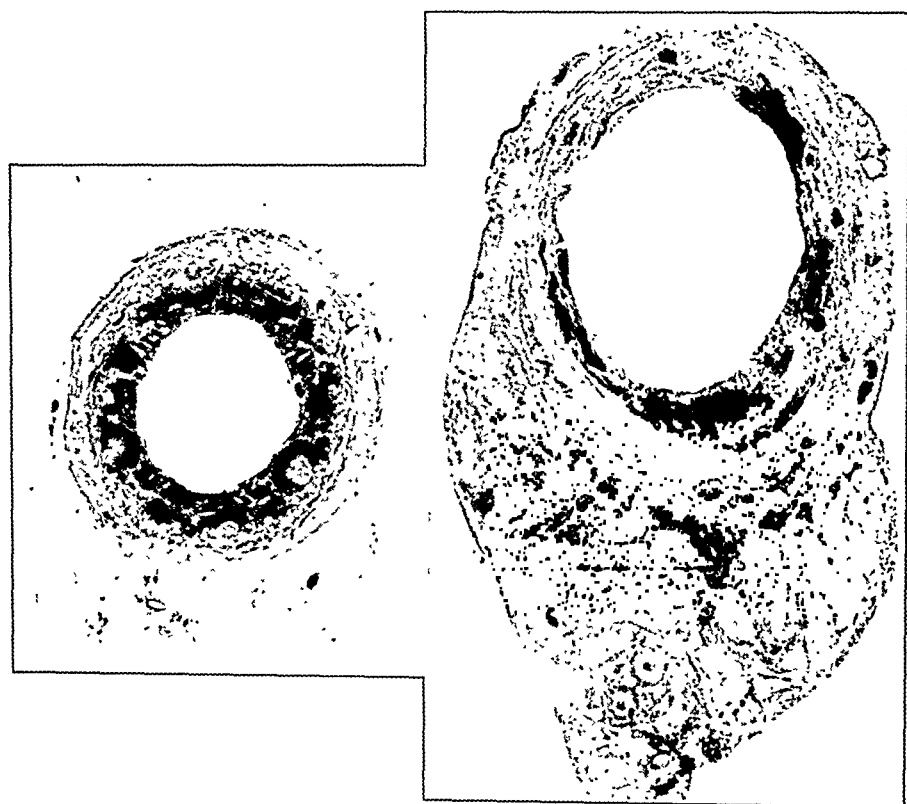


Fig. 2.—Transverse sections, same magnification, of the smaller, supernumerary and the larger, inflamed appendix.



Fig. 3.—Longitudinal sections, same magnification, through the tip of each appendix.

When the extraordinary character of the specimens was fully appreciated, further study of the material was carried out. Figure 1 is a drawing to illustrate the relative position and size of the two appendixes. Histologic examination (fig. 2) revealed that the small supernumerary appendix had the usual distribution of lymphoid tissue for this age period and both circular and longitudinal muscular coats. Histologically, therefore, it fulfilled the criteria for differentiation of this organ from a diverticulum. Sections prepared later from the two tips showed each to be complete (fig. 3), which precludes the possibility that the smaller structure was an amputated portion of the larger. Recovery was uneventful.

It is interesting to note that the last 7 examples of duplication of the appendix are strikingly similar and form a group readily separated from the "double-barreled" and "bird" types previously described. In all of them there was an appendix at the normal site and another, usually smaller, sometimes rudimentary structure protruding from the side of the cecum, generally along one of the taeniae coli, at a greater or lesser distance from the first. Whenever histologic studies have been undertaken this supernumerary structure has fulfilled the criteria which have been established for identification of an appendix.

The most satisfactory explanation for this type of the anomaly has been advanced by Cave, who saw in it "the persistence and development of a fugitive embryological structure, of great morphological interest, but one commonly ignored in standard embryological works." He referred to the "transient appendix" which was described by Kelly and Hurdon (1905) in their study of this region in over 50 human embryos from the Mall and Brödel collections. It consisted of an outgrowth from the tip of the developing cecum, which enlarges during the sixth week and atrophies toward the end of the seventh week or soon thereafter. Gladstone and Wakeley in 1924 confirmed the observations of Kelly and Hurdon in embryos of 10 to 22 mm. and gave illustrations of the "transient appendix" in sections taken at the 20 mm. stage. They pointed out that the structure simulates in its position and form the true vermiform appendix, but since it later atrophies and completely disappears it is looked on as an independent structure, not connected directly with the permanent appendix, which is differentiated later. Cave concluded that here "lies a definite potential embryological origin for the development of a supernumerary appendix, and the most plausible explanation of the specimen of appendix duplex herein described as well as of the cases quoted from the literature."

It is my opinion that while the persistence of this "transient appendix" offers a probable explanation for the third and last type of duplication described, it is likely that the other types, because of their distinct anatomic characteristics, are the result of different developmental faults.

On the other hand, it must be admitted that none of the various embryologic explanations are by any means proved; they are all quite hypothetical. In fact, one might go even further in some of the cases, such as the one described, and raise the question whether the supernumerary structure actually is an appendix. It might well be that a congenital diverticulum of the cecum, free from lymphoid tissue, as the appendix proper is at birth, could acquire this tissue in its submucosa as the appendix does and hence become identical with it. This would not be unreasonable from the biologic standpoint and may be the true explanation in this case.

In conclusion, therefore, I feel justified, as far as my case is concerned, in stating only that there existed in the patient an anomalous structure which from the surgical standpoint was another appendix and from the histologic structure was a second appendix but which may or may not have been developmentally an appendix.

#### SUMMARY

Fifteen cases of appendix vermiformis duplex, including 1 personal case, are reviewed. The anomaly is found to fall into three distinct groups, namely, the "double barrel" type (5 cases), the "bird" type (3 cases) and the "taenia coli" type (7 cases). The various embryologic explanations which have been advanced for the different forms of this anomaly are discussed.

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# IMPROVEMENT IN BLOOD TRANSFUSION SERVICE

## I. SELECTION OF TEST SERUMS; CAUSE AND PREVENTION OF HEMOLYTIC REACTIONS; ROLE OF SUBGROUPS A<sub>1</sub> AND A<sub>2</sub>

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### SELECTION OF NATURAL ANTI-A AND ANTI-B TEST SERUMS OF UNUSUALLY HIGH ISOAGGLUTININ TITER AND IMPORTANCE OF THEIR USE IN GROUPING OF BLOODS PRIOR TO TRANSFUSION

With the discovery of the human blood groups by Landsteiner<sup>1</sup> at the turn of this century, the vast majority of dangerous reactions were eliminated, and the transfusion of blood became a relatively safe procedure. Landsteiner observed that the cells of some bloods when placed with the serums of others would clump together. This phenomenon was called agglutination.<sup>2</sup> The serum factor in this phenomenon was called the agglutinin, and the cell factor was called the agglutigen. On the basis of the presence or absence of such serum and cell factors all human bloods can be classified into four groups. Landsteiner was able to divide human blood into three groups.<sup>3</sup> The fourth and rarest group was added by von Decastello<sup>4</sup> and Sturli in 1902. Three nomenclatures have been attached to the four groups, that of Jansky in 1907, that of Moss in 1910 and the "international" nomenclature accepted by the health committee of the League of Nations in 1927 (table 1).

Group AB blood contains both A and B agglutinogens and no agglutinins. Group A blood contains the A agglutigen and agglutinin *b*. Group B blood contains the B agglutigen and agglutinin *a*. Group O blood contains no agglutinogens and both *a* and *b* agglutinins.

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1. Landsteiner, K.: Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe, Zentralbl. f. Bakt. (Abt. 1) **27**:357, 1900.

2. Throughout this report the term agglutination refers to normal human isoagglutination.

3. Landsteiner, K.: Ueber Agglutinationserscheinungen normalen menschlichen Blutes, Wien. klin. Wchnschr. **14**:1132, 1901.

4. von Decastello, A.: Ueber die Isoagglutine im Serum gesunder und kranker Menschen, München. med. Wchnschr. **49**:1090, 1902.

Because of Landsteiner's observations it is now possible to pre-determine whether agglutination and a consequent reaction will occur when the blood of one person is transfused to another. This is done by the use of serums from group A and group B bloods as test serums. The serum of group A blood is known as anti-B serum, and that of group B blood is known as anti-A serum. Anti-B and anti-A serums are placed on the left and the right end, respectively, of a glass slide. Samples of the blood to be tested are placed with each puddle of test serum and observed for agglutination. Regardless of variations in the technic for this test in present use, the following interpretation is advanced.

If no agglutination is noted with either serum, the blood is classified as group O. If agglutination occurs with the anti-B serum only, the blood is classified as group B. If it occurs with the anti-A serum only, the blood is classified as group A, and if it occurs with both serums, the blood is classified as group AB.

Despite the advent of the knowledge of blood groups and the use of grouping and compatibility tests prior to transfusion, occasional severe

TABLE 1.—*Classification of Blood Groups*

International	Moss	Jansky
AB	I	IV
A	II	II
B	III	III
O	IV	I

reactions occur as a result of transfusion of incompatible blood. The mortality rate from these reactions is approximately 65 per cent. Some of the accidents may be attributed to the factor of human error. One need only peruse the literature, however, to realize that many are due to the failure of test serums in common use properly to group the blood of either the donor or the recipient in instances in which the agglutinogens are unusually weak. It is a well recognized fact that there is a marked variation in potency of both the agglutinins and the agglutinogens in the bloods of different persons.<sup>5</sup> Bloods exist in which the agglutinin tested for prior to transfusion is so weak that only the strongest test serums will show definite criteria of agglutination. The safeguard against accidents of these kinds lies in the use of test

5. Kemp, T.: Ueber den Empfindlichkeitsgrad der Blutkörperchen gegenüber Isohämagglutininen im Fötalleben und in Kindesalter beim Menschen, *Acta path et microbiol. Scandinav.* 7:146, 1930. Thomsen, O., and Kettel, K.: Die Stärke der menschlichen Isoagglutinine und entsprechenden Blutkörperchenrezeptoren in verschiedenen Lebensaltern, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 63:67, 1929. Schiff, F., and Mendlowicz, L.: Quantitative Untersuchungen über Isoagglutinine mit besonderer Berücksichtigung der Leukämie, *ibid.* 48:1, 1926.

serums of unusually potent agglutinin complement, strong enough to establish definite criteria of agglutination when placed with anticells of unusually low agglutino-gen complement.

In 1931, Coca<sup>6</sup> revealed the indifferent quality of commercial grouping serums and defined grade 1 serum as one which would in a 1:4 dilution agglutinate a 1:4 saline suspension of sensitive anticells macroscopically in one minute. Since then most commercial serums have been labeled as conforming to this standard. Because of dissatisfaction with the test serums in use at the time and the results of titrations of two commercial serums as compared to Coca grade 1 standard (table 2), a search was begun for high-titered anti-A and anti-B serums to be selected and used for future grouping tests at the Cincinnati General Hospital.

#### PROCEDURE

Samples of blood were drawn from large numbers of volunteers and tested according to the Coca method of slide titration for serum agglutinins.<sup>6</sup> Each serum was diluted 1:10 with physiologic solution of sodium chloride. A 1:4 saline suspension of each of known A and B cells was made. A measured drop of each of the suspensions was added to a drop of equal volume of each diluted antiserum on a glass slide. The time to the first macroscopic clumping was carefully noted in each instance.

#### DATA

Anti-A and anti-B serums were found which would, when diluted 1:10 with physiologic solution of sodium chloride, agglutinate a 1:4 suspension of known sensitive anticells in five seconds macroscopically<sup>7</sup> (table 2). The potency of the serums in further dilution is shown in table 3. The comparative titer of the test serums with three commercial serums bought in the open market in 1938 is shown in table 4. The method of serial titration was used. With this method progressively doubled dilutions of 0.2 cc. of the serums are mixed with a fixed amount (0.2 cc. of a 2.5 per cent suspension) of sensitive anticells. The titer of the serum is given by the reciprocal of the highest dilution at which agglutination occurs at the end of two hours. The tests were made simultaneously, and the same anticell samples were used against all serums.

#### RESULTS

Test serums of this potency have been adopted for regular use during the past four years at the Cincinnati General Hospital. Reliance now has been placed on macroscopic grouping combined with the Coca compatibility test for direct matching as reported by Ames and me<sup>7</sup> after more than 12,000 consecutive tests prior to transfusion.

6. Coca, A. F.: A Slide Method for Titrating Blood Grouping Serums, *J. Lab. & Clin. Med.* **16**:405, 1931.

7. Hoxworth, P., and Ames, A.: Blood Grouping and Compatibility, *J. A. M. A.* **108**:1234 (April 10) 1937.



## TECHNIC

Approximately 10 drops of blood is obtained by finger puncture and defibrinated in a Wassermann tube by whipping with a wooden

TABLE 2.—Potency of Anti-A and Anti-B Serums

	Serum Dilution	Cell Dilution	Time to First Macroscopic Clumping
Grade I (Coca).....	1-4	1-4	11 seconds
Commercial (1) anti-A .....	1-5	1-4	No agglutination
	None	1-4	14 seconds
Anti-B .....	1-5	1-4	No agglutination
	None	1-4	8 seconds
Commercial (2) anti-A.. ..	1-5	1-4	No agglutination
	None	1-4	16 seconds
Anti-B .....	1-5	1-4	No agglutination
	None	1-4	10 seconds
Serum at Cincinnati General Hospital, anti-A.....	1-10	1-4	5 seconds
Anti-B .....	1-10	1-4	5 seconds

TABLE 3.—Potency of the Serums in Further Dilution

	Serum Dilution	Cell Dilution	Time to First Macroscopic Clumping
Anti-A .....	1-14	1-2	20 seconds
	1-16	1-2	60 seconds
Anti-B .....	1-14	1-2	15 seconds
	1-16	1-2	50 seconds

TABLE 4.—Comparative Titers of Test Serums and Commercial Serums

Serum Titrations		Agglutination at End of Two Hours								
Dilution .....		2	4	8	16	32	64	128	256	512
Commercial (1) anti-B.....		+++	++	++	+	±				
Anti-A .....		++	++	+	+	±				
Commercial (2) anti-B.....		++	++	+++	+	+				
Anti-A .....		++	++	+	±					
Commercial (3) anti-B.....		++	++	++	++	++	+++	+++	++	+
Anti-A .....		++	++	++	++	++				
C. G. H. anti-B.....		++	++	++	++	++	+++	+++	++	+
Age 3 mo. anti-A.....		++	++	++	++	++	+++	++	+	±
		++	++	++	++	++				

applicator for five minutes. This quantity is sufficient for grouping and for several compatibility tests. Separation of cells and serum is not desirable.

*Grouping.*—Large drops of high-titered test serums anti-B and anti-A are placed on the left and the right end, respectively, of a glass slide.

Defibrinated blood is added to each drop of serum and thoroughly mixed with the aid of a platinum loop. The slide is tilted back and forth over a white background in bright light and observed macroscopically for clumping. Agglutination is striking and if serum of grade 1 (Coca<sup>6</sup>) is used will be complete in less than one minute. When no agglutination is seen after one minute on either side, the slide is placed under a Petri dish with wet blotting paper and observed again fifteen minutes later as a precaution against weak agglutinogens.

*Matching.*—A 1:1, or 50 per cent, suspension of the recipient's defibrinated blood is prepared in the stem of a white blood cell-counting pipet by drawing blood up to the 0.5 mark and then filling to the 1.0 mark with physiologic solution of sodium chloride. The blood is diluted 1:1 with saline solution because agglutination cannot be differentiated microscopically in any greater concentration and because dilution inhibits undesirable rouleau formation. The diluted blood is deposited on the left end of a glass slide and mixed by means of a jet of air blown from the pipet. An identically prepared suspension of the donor's defibrinated blood is placed on the right end of the same slide, and one fifth of this drop (two divisions of the pipet) is transferred to the drop of diluted recipient's blood. This 1:5 ratio is based on the assumption that 500 cc. is to be transfused to a patient whose blood volume is depleted 50 per cent, or approximately 2,500 cc. It provides a wide margin of safety in transfusions from a "universal" donor, as dangerously potent agglutinins will not be completely absorbed in this concentration without manifest agglutination.<sup>8</sup> The 1:5 mixture of the donor's and the recipient's blood is then stirred with a platinum loop or a glass rod, and the slide is placed under an inverted Petri dish with a piece of wet blotting paper. After fifteen minutes the mixture is again agitated and observed microscopically under low power for agglutination.

Care must be taken not to confuse rouleau formation with agglutination. The former can always be broken up by stirring, while the latter will be intensified. Agglutination will be striking if an error in grouping has been made, but a little practice is required to estimate the degree of agglutination of the recipient's cells by a "universal" donor's agglutinins in the presence of nonagglutinable cells forming rouleaux. Unless the agglutination is so definite and conspicuous that there is no question of confusion with rouleau formation, the blood may be pronounced compatible.

A recheck on the results of each grouping test at the end of fifteen minutes has been routine practice, and in no case has later agglutination appeared which was not present during the first minute. The accompany-

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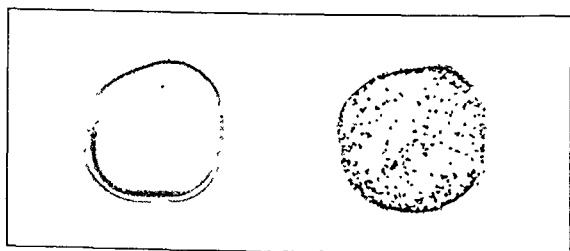
8. Levine, P., and Mabee, J.: A Dangerous "Universal" Donor Detected by the Direct Matching of Bloods, *J. Immunol.* 8:425, 1923.

ing photograph shows group A agglutination fifteen seconds after ordinarily sensitive anticells were mixed with the test serums now in use.

Occasionally, however, cells are encountered in which the agglutino-gen is very weak. This is particularly true of the A agglutinogens in bloods of group  $A_2$  and  $A_2B$ . In table 5 the action of three commercial test serums is compared with the action of anti-A serum, now in use at the Cincinnati General Hospital, when placed with a sample of group A cells of low agglutinin titer.

The necessity for use of test serums of unusual agglutinin titer in order to prevent erroneous grouping and consequent transfusion accidents cannot be overstressed. Further emphasis will be given to this subject in succeeding parts of this report.

These serums were regularly provided for all departments at the Cincinnati General Hospital, the Children's Hospital and the Christian R. Holmes Hospital for three years at a total cost of \$200 for 1,500 cc. of serums used. The cost of commercial test serums in the same



Group A agglutination fifteen seconds after the blood was mixed with the serums.

quantity would range from \$2,250 to \$6,000. Since Dec. 10, 1938, the serums have been selected in the surgical laboratories at the Cincinnati General Hospital and are distributed by the William S. Merrell Company on a nonprofit basis through agreement with the board of trustees of the University of Cincinnati. This arrangement was made in order to insure a permanent supply of the test serums in the future.

For the past four years the same two donors have supplied all the anti-A and anti-B test serums used. However, donors whose serums excel the requirements of Coca's grade 1 and particularly those who meet the aforementioned standards are rare, and finding them is accomplished only after considerable search. Consequently, methods for concentrating the hemagglutinins in serum may be highly desirable to insure an unlimited supply. Artificial concentration by alternate freezing and thawing was reported by Terry.<sup>9</sup> The lyophile method of drying

9. Terry, M. C.: High-Titer Blood Grouping Serum, *Proc. Soc. Exper. Biol. & Med.* **33**:14, 1935.

serum as reported by Flosdorf and Mudd<sup>10</sup> was utilized by Mahoney and me<sup>11</sup> to accomplish the same purpose. This was done by redissolving dried serum in less than the original volume. The resulting product was found to have a hemagglutinin titer in inverse proportion to the reduction in volume and to be suitable for use as test serum.

#### CAUSE AND PREVENTION OF HEMOLYTIC BLOOD TRANSFUSION REACTIONS

Many of the untoward accidents which follow the transfusion of incompatible blood are of the delayed or hemolytic type, resulting from hemolysis of the cells of the donor or those of the recipient in the blood stream. The clinical and pathologic pictures in cases of hemolytic transfusion reaction have been lucidly described by Bordley<sup>12</sup> and by Baker and Dodds.<sup>13</sup> The syndrome is usually characterized by a sharp febrile reaction within a few hours of the transfusion. This may or may not be distinguished by signs of immediate reaction or followed by jaundice.

TABLE 5.—Group *A<sub>2</sub>* Blood With Cell Factor of Low Titer (Equal Parts Whole Blood and Serum)

Anti-A Commercial Serum	Time to Macroscopic Agglutination in Minutes						
	1	2	3	4	5	10	15
1 .....	0	0	0	0	0	0	±
2 .....	0	±	+	+	+	+	++
3 .....	0	0	0	0	±	±	+
C. G. H. Anti-A serum.....	+	+	++	++	++	++	+++

Hemoglobinuria and oliguria or anuria follow. Suppression of urine continues for several days, accompanied with the signs, symptoms and laboratory findings associated with progressive uremia. Uremic death occurs or a diuretic recovery begins on the fourth to the eighteenth day. The mortality rate was approximately 65 per cent in 42 reported cases. The autopsy observations are central lobular necrosis of the liver and pale, edematous kidneys, with degenerative changes in all tubular epithelium.

It has been shown in the laboratory that isohemolysins correspond in specificity to the isoagglutinins which are normally present in serum.

10. Flosdorf, E. W., and Mudd, S.: Procedure and Apparatus for Preservation in "Lyophile" Form of Serum and Other Biological Substances, *J. Immunol.* **29**: 389, 1935.

11. Hoxworth, P., and Mahoney, E.: Artificial Concentration of Test Serums in Blood Grouping, *J. A. M. A.* **111**:1554 (Oct. 22) 1938.

12. Bordley, J.: Reactions Following Transfusion of Blood, with Urinary Suppression and Uremia, *Arch. Int. Med.* **47**:288 (Feb.) 1931.

13. Baker, S. L., and Dodds, E. C.: Obstruction of the Renal Tubules During the Excretion of Haemoglobin, *Brit. J. Exper. Path.* **6**:247, 1925.

Hemolysins occur in about 30 per cent of the cases in which it would be expected according to the Landsteiner rule of the blood groups if fresh testing serum is used.<sup>14</sup> If the testing serum used, however, has been stored in an ice box for about two weeks it will become inactivated as far as hemolysins are concerned.<sup>14</sup> On the test slide agglutination always precedes hemolysis, but the one phenomenon may be more apparent than the other. Agglutination usually predominates, but in rare instances hemolysis may be the more pronounced, preceded only by a very transient agglutination phase. Under such circumstances hemolysins are of practical importance, because they may mask true agglutination and lead to errors in blood grouping. It has been shown that it is the serum factor which determines the predominance of agglutination or hemolysis when incompatible cells are added.<sup>14</sup> Therefore, by selection of a high-titered test serum free of hemolysins one can predetermine most incompatibilities, whether the incompatibilities are evidenced by agglutination or hemolysis.

The presence of atypical agglutinins in the serum of either the donor or the recipient will be detected on careful performance of a direct match test after the groups of the bloods to be mixed in transfusion are determined. Atypical agglutinins not conforming to the behavior of the blood groups of Landsteiner must be extremely rare, since in examination of the last 3,000 consecutive bloods prior to transfusion at the Cincinnati General Hospital there was not a single instance in which two bloods of the same group did not show perfect compatibility when the direct match was made. Forty-two cases of hemolytic transfusion reaction are analyzed in the following studies; the presence of atypical agglutinins has been adequately demonstrated in only 4. In 38 cases, as will be shown to be true in the case reported by McCandless from this clinic, the accidents may have resulted from failure of the test serums in use properly to detect weak agglutinogens, thereby leading to errors in grouping or to atypical hemolysins.

In 1930, Bordley<sup>12</sup> presented a series of 17 cases of hemolytic transfusion reaction, 3 of which were his own. McCandless<sup>15</sup> collected 9 additional cases from the later literature and added 1, making a total of 27. Fifteen cases reported since then are added here, making a total of 42 cases in which laboratory data are analyzed. In many of these cases the reactions were admittedly due to errors in grouping and compatibility later discovered on recheck by the authors. If the criteria of agglutination had been more promptly and clearly defined at the time of

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14. Wiener, A. S.: *Blood Groups and Blood Transfusion*, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

15. McCandless, H. G.: A Hemolytic Blood Transfusion Reaction with Oliguria, *J. A. M. A.* **105**:952 (Sept. 21) 1935.

the first test, most of these would have been prevented. In other cases recheck by ordinary methods of grouping and compatibility showed the donor's and the recipient's blood to be of the same group. In these instances the reactions are either unexplained or attributed to the presence of agglutinins and hemolysins which are atypical in their behavior.

Wiener and Peters<sup>16</sup> reported 2 cases of intragroup hemolytic transfusion reaction in which agglutination of the donors' cells with the patients' serums was demonstrable on chilling but not at room temperature. Further tests of these serums against cells of group O bloods taken at random revealed agglutination reactions coinciding with those given by antirhesus immune rabbit serum as described by Landsteiner and Wiener. On the basis of the behavior of cells when placed with antirhesus serums, all human bloods were classified by Wiener as Rh + or Rh —. In these 2 cases the hemolytic transfusion reactions were explained by Wiener and Peters as due to the transfusion of Rh + blood to subjects with Rh — blood, resulting in the formation of anti-Rh immune antibodies in the serums of the patients which hemolyzed the donors' cells. In their report methods are given for the prevention of hemolytic reactions due to Rh factors. In a possible hemolytic transfusion reaction which occurred in the series of 3,077 transfusions of bank blood at the Cincinnati General Hospital the blood of the recipient was Rh + and that of the donor was Rh — as determined by Wiener on samples sent to him. The Rh complex could not, therefore, have played any part in this reaction.

#### DATA

In the following statistical analysis of laboratory data in the 42 cases reported, tables 7 to 19 group the cases according to the degree of completeness with which they were studied from the laboratory standpoint. This facilitates comment on the evident facts.

TABLE 6.—*No Record of Grouping or Compatibility Tests Before or After Transfusion (2 Cases)*

Case and Author
1. Goormaghtigh, N.: Arch. méd. belges 72: 611, 1918
2. Santy, J. P.: Lyon chir. 23: 608, 1926

#### COMMENT

In 2 cases there was no record of grouping or the compatibility tests.

16. Wiener, A. S., and Peters, H. R.: Hemolytic Reactions in Transfusions of Blood of the Homologous Group with Three Cases in Which Agglutinin Was Responsible, Ann. Int. Med. 13:2306, 1922

TABLE 7.—*Errors in Both Grouping and Compatibility Found on Recheck (7 Cases)*

Case and Author	Error	Recheck
1. Bordley, <sup>12</sup> .....	A to A	A to O
2. Lindau, A.: Acta path. et microbiol. Scandinav. 5: 382, 1928.....	O to O	A to O
3. Goldring, W., and Graef, I.: Arch. Int. Med. 58: 825 (Nov.) 1936.....	O to O	A to O
4. Goldring, W., and Graef, I.: Arch. Int. Med. 58: 825 (Nov.) 1936.....	O to O	A to O
5. Goldring, W., and Graef, I.: Arch. Int. Med. 58: 825 (Nov.) 1936.....	O to O	A to O
6. Younge, P. A.: New England J. Med. 214: 879, 1936.....	O to O	A to O
7. Bordley, <sup>12</sup> .....	O to O	O to A

# COMMENT

Seven reactions were admitted by the authors to be due to errors in both grouping and compatibility found on recheck. Four of the cases were reported in the recent literature, and from the authors' description it is obvious that more immediate criteria of agglutination, such as would have been afforded by the use of testing serums of higher titer, would have prevented these accidents.

TABLE 8.—*Grouped as Identical Prior to Transfusion and on Recheck; Compatible Before Transfusion; Donors' Cells Incompatible on Recheck (Four Cases)*

Case and Author	Group Recipient and Donor		Compatibility	
	Before Transfusion	Recheck	Cells of Donor Before Transfusion	Serum of Recipient on Recheck
1. Shera, G.*: Brit. M. J. 1: 754, 1928.....	0	0	—	+
2. Baker and Dodds, <sup>13</sup> .....	0	0	—	+
3. Copher, G. H.: Arch. Surg. 7: 125 (July) 1923.....	0	0	—	+
4. Parr, L. W., and Krischner, H.**: J. A. M. A. 98: 47 (Jan. 2) 1932.....	0	0	—	+

\* Author believed his Anti-A test serum would not agglutinate the cells of this "A" donor. Donor's cells agglutinated in 65 minutes on recheck of compatibility.

\*\* Slow hemolysis of donor's cells.

TABLE 9.—*No Grouping; Compatible Before Transfusion; Donor's Cells Incompatible on Recheck (Two Cases)*

Case and Author	Compatibility	
	Before	Recheck
1. Baker and Dodds, <sup>13</sup> .....	—	+
2. Johnson, R. A., and Conway, J. F.: Am. J. Obst. & Gynec. 26: 255, 1933..	—	+

TABLE 10.—*Grouped Before Transfusion; No Recheck; Compatible Before; Donor's Cells Incompatible on Recheck (One Case)*

Author	Group	Compatibility Donor's Cells	
		Before	Recheck
Younge, P. A.: New England J. Med. 214: 879, 1936.....	A to A	—	+

## COMMENT

The 7 accidents due to erroneous interpretation of compatibility tests found on recheck may have been due to failure of the test serum in use to agglutinate low-titered cell factors or to atypical hemolysins. It is significant that in 4 of these cases all bloods were grouped as O. In none of the cases of this group was the titer of the test serum used stated by the authors.

TABLE 11.—*Identical Groups; Rechecked; No Compatibility Tests (Two Cases)*

Case and Author	Group
1. Jemke, R.: Virchows Arch. f. path. Anat. 257: 415, 1925.....	A to A
2. Goldring, W., and Graef, I.: Arch. Int. Med. 58: 825 (Nov.) 1936.....	O to O

TABLE 12.—*Group Not Determined; Compatible Before Transfusion and On Recheck (Four Cases)*

Case and Author	Donor's Cells		Recipient's Cells	
	Prior	Recheck	Prior	Recheck
1. Boïdin, Berthaux and Beyrand: Bull. et mém. Soc. méd. d. hôp. de Paris 43: 869, 1919.....	—	—	—	—
2. Curtis, A. H.: Surg., Gynec. & Obst. 30: 627, 1920.....	—	—	—	—
3. Stewart, S. G.: M. Clin. North America 15: 553, 1931....	—	—	—	—
4. Sinclair, A. S.: Canad. M. A. J. 35: 423, 1936.....	—	—	—	—

In each of these cases the titers of two unknown serums were depended on.

TABLE 13.—*Only Recipient Grouped Before Transfusion; No Recheck; Compatible Prior to Transfusion; No Recheck (Two Cases)*

Case and Author	Group of Recipient	Compatibility	
		Donor's Cells	Recipient's Cells
1. Bordley, 12 .....	O	—	—
2. Goldring, W., and Graef, I.: Arch. Int. Med. 58: 825 (Nov.) 1936 .....	O	—	—

TABLE 14.—*No Record of Grouping; Both Recipient's and Donor's Cells Compatible; No Recheck*

Author
Bancroft, F. W.: Ann. Surg. 51: 733, 1925.

## COMMENT

In 9 cases the ordinary precautions of performing both grouping and compatibility tests prior to transfusion were not observed. Grouping only was done in 2 of these cases (table 12). In 7, only compatibility tests were made and the titer of an unknown test serum was depended on. The titers of the test serums were not stated in those cases which were grouped.



TABLE 15.—*Groups Determined Before Transfusion; No Recheck; Compatible Before Transfusion; No Recheck (Three Cases)*

Case and Author	Group	Compatibility	
		Donor's Cells	Recipient's Cells
1. Ollensis, A. E.: M. J. & Rec. <b>128</b> : 178, 1928.....	"Same Group"	—	—
2. Witts, L. J.: Lancet <b>1</b> : 1297, 1929.....	A to A	—	—
3. Goldring, W., and Graef, I.: Arch. Int. Med. <b>58</b> : 825 (Nov.) 1936 .....	O to O	—	—

#### COMMENT

The 3 cases in table 15 may be subjected to the same criticism as those of table 18.

TABLE 16.—*"Universal" Donor Employed; Donor's Cells Compatible (One Case)*

Author	Group of Recipient	Group of Donor
de Gowin, E. L.*: J. A. M. A. <b>108</b> : 296 (Jan. 23) 1937.....	AB	O

\* The *a* agglutinin of the donor was potent in a 1:80 dilution. In this instance the use of a group A or B donor with a low-titred serum factor would have avoided the reaction.

#### COMMENT

This accident was reported in the recent literature and was admittedly due to the indiscriminate use of a universal donor. The routine use of the Coca compatibility test, as described later in this report as a method for direct matching, prevents such an occurrence. The fact that the agglutinins in the donor's serum were potent in a 1:80 dilution means that a marked incompatibility would have revealed itself in this quantitative test.

TABLE 17.—*Atypical Agglutinins Demonstrated (Four Cases)*

Case and Author	
1. Culbertson, O. G., and Ratcliffe, A. W.: Am. J. M. Sc. <b>192</b> : 471, 1936	Identical groups (O) rechecked; atypical agglutinin demonstrated in serum of recipient
2. Ottenburg, R., and Johnson, A.: J. Immunol. <b>12</b> : 35, 1926	Identical groups (B); atypical agglutinin demonstrated in serum of donor
3. Wiener and Peters. <sup>16</sup>	Identical groups (O); atypical agglutinin (anti-Rh) demonstrated in serum of recipient
4. Wiener and Peters. <sup>16</sup>	Identical groups (A); atypical agglutinin (anti-Rh) demonstrated in serum of recipient

#### COMMENT

In 4 cases atypical agglutinins were adequately demonstrated. Use of a compatibility test prior to the transfusion, instead of reliance solely on the grouping test, may have prevented the giving of two of these

transfusions. The others could have been avoided by the method suggested by Wiener.<sup>15</sup>

TABLE 18.—*Grouped as Identical Prior to Transfusion and On Recheck; Compatible Before and On Recheck (Nine Cases)*

Case and Author	Group
1. Lindau, A.: <i>Acta path. et microbiol. Scandinav.</i> <b>5</b> : 382, 1928.....	?
2. Payne, R. V.: <i>Guy's Hosp. Rep.</i> <b>84</b> : 65, 1931.....	O to O
3. Von Deesten, H. T., and Cosgrove, S. A.: <i>Ann. Int. Med.</i> <b>7</b> : 105, 1933.....	A to A
4. Johnson, R. A., and Conway, J. F.: <i>Am. J. Obst. &amp; Gynec.</i> <b>26</b> : 255, 1933....	?
5. Johnson, R. A., and Conway, J. F.: <i>Am. J. Obst. &amp; Gynec.</i> <b>26</b> : 255, 1933....	O to O
6. Stewart, S. G.: <i>M. Clin. North America</i> <b>15</b> : 553, 1931.....	O to O
7. Baron, O.: <i>Kentucky M. J.</i> <b>30</b> : 326 (1932).....	O to O
8. McCandless,* <sup>15</sup> .....	O to O
9. Goldring, W., and Graef, I.: <i>Arch. Int. Med.</i> <b>58</b> : 825 (Nov.) 1936.....	O to O

\* Cincinnati General Hospital.

#### COMMENT

In 9 cases the accidents were listed as unexplained because in each the bloods of the donor and the recipient were grouped and matched both prior to and after transfusion. They were found to be of the same group and compatible each time. In each of these reports the authors did not discuss the titer of the test serums used, and none offered evidence to contradict the explanation of a low-titered cell factor. That the test serums used in these cases may have failed to show the true group of the blood owing to weak agglutinogens is indicated by the fact that in all except 3 cases the bloods were grouped as O. (The group was not stated in 2 reports.) The case reported by McCandless belongs to this group. The clinical picture was typical of a hemolytic blood transfusion reaction.

The blood groups of the donor and the patient were determined as group O before transfusion. The test serums used would agglutinate ordinarily sensitive anticells readily and were in routine use at that time for the testing of bloods prior to transfusion in all cases in the surgical service at the Cincinnati General Hospital. A direct match of the donor's and the patient's bloods showed no agglutination at the end of one-half hour. Rechecks on the blood groups of these 2 persons were made eight and twelve days after the transfusion. The same test serums were used in both rechecks as were used in the original test. Direct match during the recheck examinations showed no cross agglutination at the end of eight hours.

In his report, McCandless<sup>15</sup> concluded that this hemolytic transfusion reaction was due to an anomalous or atypical hemolysin present in the serum of the recipient which did not obey the rule of the Landsteiner blood groups and caused hemolysis of the donor's cells in the recipient's blood stream.

Two years later, after the selection and adoption for routine use of unusually high-titered anti-A and anti-B test serums in the grouping of blood prior to transfusion, the bloods involved in McCandless' case were restudied. The blood of the patient was grouped as O, showing no agglutination with either the anti-A or the anti-B test serum. The blood of the donor was grouped as A, agglutination occurring with the anti-A test serum in fifty seconds to such a marked degree that it could be seen readily with the naked eye. Ordinarily sensitive group A cells showed the same degree of agglutination when placed with this test serum in less than five seconds. A direct match between the donor's and the patient's bloods showed no cross agglutination at the end of eight hours.

On the basis of these data one can only conclude that the cause for this hemolytic transfusion reaction was not an atypical hemolysin in the serum of the blood of the recipient. The cause was the failure of a test serum which had proved satisfactory in the grouping of the usual bloods properly to group the blood of the donor. The *a* agglutinin in the serum of the recipient also failed to agglutinate the anticells in the blood of the donor. This explains the absence of agglutination in a direct match between the two bloods concerned. The agglutinin A present in the donor's blood cells was of such low titer that it could only be shown with test serums of unusually high titer.

#### SUMMARY AND CONCLUSIONS

Although the explanation for the cause of the hemolytic transfusion reaction in McCandless' case is not the explanation for the reactions in all of the 42 cases analyzed in the foregoing paragraphs, it is significant that the titer of the test serum used was not reported in 40 of the 42 case reports. The frequency of occurrence of blood group O in both the patient and the donor in these case reports is also significant, because it is in group O bloods only that no agglutination occurs when anti-A and anti-B test serums are placed with the cells of these bloods.

The blood of McCandless' donor proved to be of subgroup  $A_2$ , as might be expected, since the agglutinogens of this subgroup are known to be weak. The significance of subgroups  $A_1$  and  $A_2$  in transfusion reactions will be considered in succeeding pages.

Certainly the evidence presented indicates that test serums frequently accepted as adequate in many hospitals for grouping the usual blood lack the necessary potency for grouping the unusual blood in which the agglutinin is of extremely low titer. Such errors will be detected by compatibility tests only if the antisera are by chance of high potency.

Atypical agglutinins which do not conform to the behavior of agglutinins *a* and *b* occur rarely. Before any hemolytic transfusion reaction is attributed to such a qualitative factor, the bloods concerned should be

subjected to an adequate study from the quantitative standpoint. Weak agglutinogens will be detected by testing with serums of high agglutinin potency.

#### ROLE OF SUBGROUPS $A_1$ AND $A_2$ IN TRANSFUSION REACTIONS

In 1910 von Dungern and Hirschfeld<sup>17</sup> showed that when a group B serum was absorbed with group A cells the group B serum lost its power to agglutinate some group A cells but retained its power to agglutinate others. On the basis of these observations, they suggested a subdivision of group A into groups  $A_1$  and  $A_2$  and of group AB into groups  $A_1B$  and  $A_2B$ . These observations were later confirmed and substantiated by many other workers.

Certain authors<sup>18</sup> have contended that the subgroups of A may be responsible for transfusion reactions for the following two reasons: (1) because they may be incompatible with each other and (2) because the subgroups  $A_2$  and  $A_2B$  are characteristically weak in agglutinin A and may not be detected except with test serums of unusually high anti-A titer. There is no difference in opinion among observers about the latter factor playing a part in transfusion accidents. Without test serum of unusually high titer, blood of group  $A_2$  is frequently erroneously grouped as O because of the failure of the A cells to agglutinate, and blood of group  $A_2B$  is frequently erroneously grouped as B for the same reason. Obviously such errors in grouping may not be revealed by compatibility tests, for the same reason that the bloods were erroneously grouped. That is, the anti-A agglutinin in the group O or group B blood with which the direct match was made would not be sufficiently potent to cause agglutination, and the direct match would be read as compatible. Reports of mistakes of this kind are frequent in the literature. The accident erroneously reported by McCandless as due to an atypical hemolysin is an example from the Cincinnati General Hospital.

There is much doubt, however, concerning the opinion that incompatibility between groups  $A_1$  and  $A_2$  and groups  $A_1B$  and  $A_2B$  may be responsible for transfusion reactions. Some writers<sup>19</sup> have said that the difference between  $A_1$  and  $A_2$  is only quantitative and not qualitative and that the  $A_2$  factor is merely weaker than the A factor. They have supported their argument with the fact that all anti-A agglutinin may

17. von Dungern, E., and Hirschfeld, L.: Ueber gruppenspezifische Strukturen des Blutes, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 8:526, 1911.

18. (a) Davidsohn, I.: A Method for Recognition of Blood Subgroups  $A_1$  and  $A_2$ , *J. A. M. A.* 112:713 (Feb. 25) 1939. (b) Blinow, N. I.: Subgroups  $A_1$  and  $A_2$  and Their Practical Significance, *Sovet. khir.* 7:335, 1934.

19. Lattes, L.: *Individuality of the Blood*, New York, Oxford University Press, 1932, p. 72. Friedenreich, V.: Ueber die Serologie der Untergruppen  $A_1$  und  $A_2$ , *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 71:283, 1931.

be washed from a given serum if sufficient  $A_2$  cells are added, although it may take a much greater quantity of  $A_2$  cells to absorb the serum.

Those authors who contend that there is a qualitative difference between groups  $A_1$  and  $A_2$  offer the following evidence to support their contentions. One of them De Gowin<sup>20</sup>) listed three fatal transfusion reactions in patients with blood of group A given transfusions with blood of the same group. Another of de Gowin's patients received five blood transfusions. The patient's blood was group A; the blood of all five donors was group A; reaction followed the first three transfusions, and none followed the next two. This is not necessarily evidence of incompatibility between subgroups of A. The reactions he described, such as chills and fever, are frequently observed between members of other groups and even after intravenous injection of dextrose or saline solution.

Blinow<sup>18b</sup> reported a higher incidence of transfusion reactions between members of blood group A than between members of other groups. He also analyzed the subgroups and noted instances in which patients of group  $A_1$  received group  $A_1$  blood without reaction but had reactions regularly when blood of subgroup  $A_2$  was transfused. Blinow also noted reactions of mild and moderate severity characterized by chills and fever when the subgroups of the donor and those of the recipient were identical.

Some writers<sup>21</sup> support their contention of the qualitative difference between the subgroups of A by the fact that they have been able occasionally to demonstrate agglutinin  $a_1$  in subgroup  $A_2$  and agglutinin  $a_2$  in subgroup  $A_1$ . Agglutinin  $a_1$  agglutinates the cells of subgroup  $A_1$  and  $A_1B$ . Agglutinin  $a_2$  is very rare, according to these authors; it will agglutinate the cells of  $A_2$  and  $A_2B$  and, in addition, will agglutinate the cells of O. These workers only in rare instances have been able to demonstrate this phenomenon at room temperature and only in even rarer instances have they been able to demonstrate it at body temperature. There are various theories for the explanation of these phenomena, notably by Thompsen, Landsteiner, Lederer and Wiener, and the study of these factors is undergoing considerable investigation at present.

Evidence to support the contention that transfusion reactions result from incompatibility between the subgroups of A appears to be inadequate. The mild and moderately severe reactions characterized only by chills and fever at the Cincinnati General Hospital occur just as often between members of other groups as between members of group A. To conclude that reactions of this nature are due to incompatibilities between

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20. DeGowin, E. L.: Grave Sequelae of Blood Transfusions, *Ann. Int. Med.* **11**:1777, 1938.

21. Landsteiner, K., and Witt, D. H.: Observations on Human Isoagglutinins. *Proc. Soc. Exper. Biol. & Med.* **21**:389, 1924.

subgroup  $A_1$  and  $A_2$  is again hardly justified, since they occur after intravenous administration of saline and dextrose solutions. They may be attributable to various factors, such as contaminants from glassware, rubber tubing and citrate, pyrogenic substances and incipient coagulative changes in blood. The demonstration of incompatible agglutinins between group  $A_1$  and group  $A_2$  bloods is only evidence on a glass slide, and, as these agglutinins show definite relation to cold agglutinins, they may well have no significance in transfusion reactions.

It can be stated that, despite arguments for incompatibility between group  $A_1$  and group  $A_2$  bloods and their responsibility for transfusion reactions, there is not a single report in the literature in which slide evidence of incompatibility between members of subgroup  $A_1$  and subgroup  $A_2$  bloods has been demonstrated either before or after a severe or fatal hemolytic reaction has occurred as the result of the transfusion. DeGowin and others have recorded cases of slide evidence of incompatibility following severe and fatal reactions between members of group A, but there is no report of the subgroups involved. Hemolytic transfusion reactions between members of other groups which are identical, groups other than A, do occur, and the reaction in DeGowin's cases might just as easily be due to atypical agglutinins as to incompatibilities between subgroups  $A_1$  and  $A_2$ . It would seem reasonable to state that the reactions occurring between members of group A could not be attributed to incompatibilities between subgroups if the percentage of reactions occurring between members of group A was about the same as the percentage of reactions occurring between members of other groups, when compared in a large series of cases studied on the statistical basis of the frequency of reactions. In the last 3,077 consecutive blood transfusions at the Cincinnati General Hospital there has been no significant increase in the incidence of reactions between members of group A as compared to members of other blood groups.

# SOME UNUSUAL TUMORS OF THE CERVICAL REGION

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Tumors of the face and neck, either inflammatory or neoplastic, are readily and frequently recognized early in their development because of the direct or mirrored asymmetries, disfigurements and symptoms they produce. Although they become evident in their incipiency, their "status quo" may often belie the extent of their spread and fail to betray the site of their origin. They may furtively appear with shocking suddenness or languidly ascend from an extensive growth hidden from view for a considerable time. Accordingly, while such tumors are frequently detected early, they always constitute a serious clinical and surgical problem.

As has been pointed out (Boyd,<sup>1</sup>), a certain degree of "regional classification may be of value." Midline tumors are frequently congenital; tumors of the anterior triangle are either metastatic carcinomas or tumors of the salivary glands; tumors of the posterior triangle are often primary tumors of the lymph nodes, such as lymphosarcoma and the lesions of Hodgkin's disease.

In addition to the common tumors that are frequently found in the region of the neck, there are inflammatory or pseudoneoplastic enlargements which complicate the diagnosis.

Tumors of the face, both external and internal, tend to give rise to secondary extensions that involve the submental surfaces of the neck or the upper group of cervical nodes, while tumors originating in the chest or in the abdomen tend to spread into the lower cervical nodes. However, as has been pointed out (Boyd), it is occasionally noted that secondary metastases may skip one set of nodes and lodge in a more

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Read at a meeting of the Pacific Coast Surgical Society, April 6, 1940.

From the Departments of Surgery and Pathology of the University of Oregon Medical School.

1. Boyd, W.: Tumors and Cysts of the Neck, Tr. West. S. A. (1938) 48:172, 1939.

distal group, so that the site of origin may remain undiscovered. When such a state obtains, a primary site in the pharynx may give rise to metastasis in a supraclavicular node, while a new growth in the chest may appear in a submental or an upper cervical node.

In addition to the commonly known and well recognized tumors of the cervical region, there are a number which occupy the same region and have similar sources but are relatively uncommon. Such neoplasias often clinically simulate in every respect those commonly seen, but they differ markedly in pathologic pattern, so that their exact nature is not

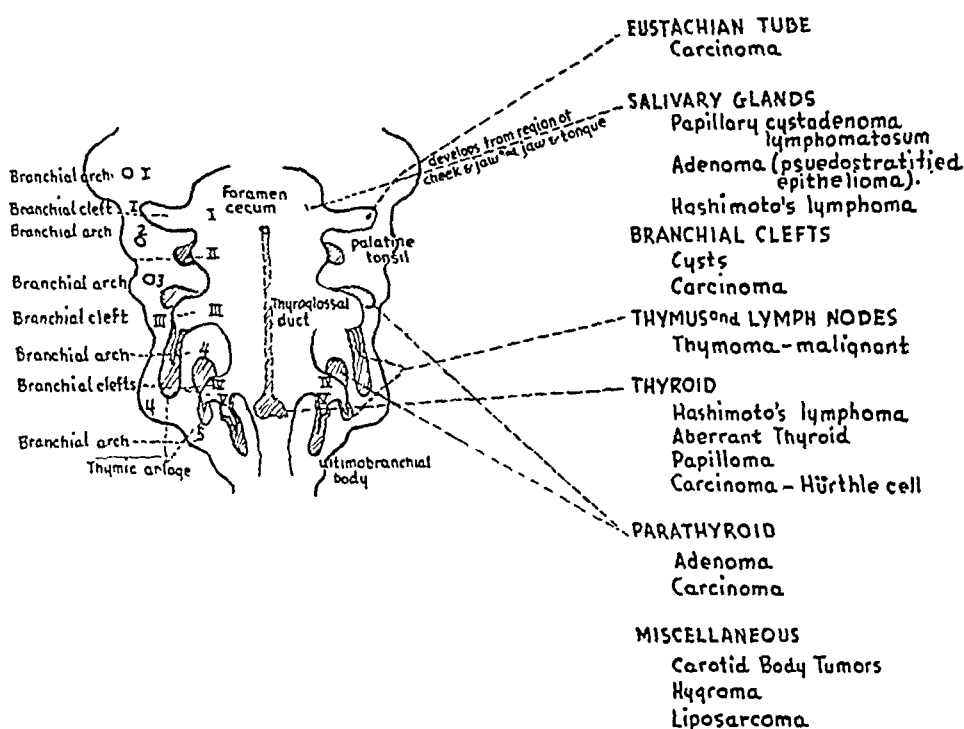


Fig. 1.—Drawing of the developmental formations of the foregut, with indications of the sources of uncommon tumors.

determined, and misleading diagnoses may greatly alter the clinical course and the prognosis.

These relatively infrequent tumors appear to be definite manifestations of abnormalities of development of the caudal end of the foregut with its numerous clefts and folds. In some instances they may be marked manifestations of responses to functional demands resulting in disarrangements and tumefactions with possible abnormal spread. In others they appear to be definite neoplasias, both benign and malignant, that spring from aberrant cell rests or later structural formations (fig. 1).



Such tumors as these may be grouped according to their possible site of origin as follows:

Primary carcinoma of the eustachian tube

Primary tumors of the salivary glands

(a) Papillary cystadenoma lymphomatosum

(b) Pseudoadenomatous epithelioma (benign)

(c) Massive lymphocytic salivary adenitis (Hashimoto's disease)

Tumors of the branchial cleft

(a) Pseudoadenomatous epithelioma (benign)

(b) Branchiogenic carcinomas

Tumors of the thymus and other unusual growths involving lymph channels or nodes

(a) Malignant thymoma

(b) Hygroma

Tumors of thyroid or parathyroid origin

(a) Riedel's struma

(b) Hashimoto's disease

(c) Aberrant thyroid

(d) Hürthle cell carcinoma

(e) Adenomas of the parathyroid

(f) Adenocarcinoma of the parathyroid

(g) Liposarcoma

Miscellaneous tumors

(a) Tumor of the carotid body

(b) Ganglioneuroma

(c) Schwannoma

(d) Liposarcoma, recurrent

(e) Rhabdomyosarcoma

Some of these tumors have been observed by us, and their salient clinical and pathologic characteristics are recorded here.

#### GROUP 1: PRIMARY TUMORS OF THE SALIVARY GLANDS

The common tumors of the salivary glands occur most frequently in the parotid gland as the so-called mixed tumors (McFarland<sup>2</sup>). Although their incidence, clinical course and complex cytologic structure are well known, their origin is still obscure. In addition to these well recognized pathologic entities in the salivary glands, occasionally

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2. McFarland, J.: Three Hundred Mixed Tumors of Salivary Glands, of Which Sixty-Nine Recurred, Surg., Gynec. & Obst. **63**:457 (Oct.) 1936.

one encounters tumors that are even more extraordinary and complex. The following cases are submitted because of the odd embryologic patterns observed.

CASE 1.—C. G. V., a man aged 68, was admitted to the hospital to the service of Dr. E. W. Rockey, complaining of an inactive, painless swelling the size of a "small hen egg" on the left side of the neck, below the angle of the jaw. It was regarded as a mixed tumor of the parotid gland and was removed. It contained about  $\frac{1}{2}$  ounce (15 cc.) of creamy material. The pathologist (Dr. Charles Manlove, of the Good Samaritan Hospital) described the tumor as measuring 5.5 by 4 by 2.5 cm. and weighing 23 Gm.; it was round to oval, brownish red, friable and partially cystic. Microscopic sections disclosed a new growth with a papillary structure having the epithelial cells in multiple; pseudostriated layers



Fig. 2 (case 2, group 1).—Gross appearance of a papillary cystadenoma lymphomatosum of the parotid.

resembling those of the respiratory tract. The stroma was characterized by numerous lymphoid cells with definite germinal follicles. The tumor was recognized as a benign cystic papilloma of branchial cleft origin. Apparent recovery was prompt, but the patient was readmitted five and one-half months later, with a small lump just below and anterior to the ear. This had appeared two months after he left the hospital. The second growth (size of a filbert) was definitely encapsulated and occupied the lower pole of the parotid gland. The tumor weighed 4.5 Gm. and had a compact structure similar to that of the first tumor grossly and microscopically. Sections were submitted to one of us (F. R. M.). Dr. Warren Hunter aided in recognizing the character of the tumor, having seen a similar lesion reported by Warthin<sup>2a</sup> as a rare teratoid of the parotid region and designated by him as papillary cystadenoma lymphomatosum. There has been no recurrence.

2a. Warthin, A. S.: Papillary Cystadenoma Lymphomatosum: A Rare Teratoid of the Parotid Region, *J. Cancer Research* 13:116 (July) 1929.

CASE 2.—J. M. N., a white man aged 40, was admitted to the hospital for treatment of a tumor of three years' duration on the left side of the neck. Three months prior to his admission to the hospital it had begun to grow rapidly. The tumor was found just posterior to the angle of the jaw and had reached the size of a "small hen egg." It was soft, not tender, smooth and movable. There was no cervical adenopathy or loss of weight. The diagnosis was tumor of the left



Fig. 3 (case 2, group 1).—Photomicrograph illustrating the papillary pattern as well as the intensive lymphoid infiltration of the stroma.

jaw, probably cystic. After removal, it was referred to one of us (F. R. M.). It was found to be covered with a smooth, fascia-like envelope and measured 5 by 4 by 2 cm. It had a brown discoloration similar to that produced by blood pigment. There were also smooth areas that contained a pale, soft, putty-like material (fig. 2). Sections revealed a typical papillary structure with definite lymphatic accumulations and germinal follicles similar to those seen in the tumor in case 1. At present there has been no recurrence (fig. 3).

CASE 3.—P. C., a man aged 42, was admitted to the hospital on Aug. 21, 1938, for removal of a cyst on the left side of the face. The cyst was removed at another institution and was seen by one of us. It measured 2.5 by 2 by 1.2 cm.; it was composed of an irregular, friable, brownish yellow substance within a necrotic medium. Microscopic sections disclosed well differentiated small acini with ducts and columnar epithelium having the histologic structure of the parotid gland. In certain areas, however, there was papillary proliferation, the cells covering the acini having an embryonic malignant pattern that obliterated the acini. The tumor was designated as a papillary adenocarcinoma of the parotid gland. After the removal, 550,000 r units of high voltage roentgen therapy was given, in spite of



Fig. 4 (case 3, group 1).—Photograph of the tumor (B), including the salivary gland (A) and a portion of muscle (C).

which a definite recurrence developed seven months later. Radical resection with implantation of radon seeds was carried out. The tissue removed measured 8 by 5 by 3 cm. (fig. 4). It was covered with a fascia-like investment; it was lobulated and whitish and included the submaxillary gland with the attached lymph nodes. Microscopically this tumor had an appearance similar to those in cases 1 and 2 except for absence of the lymphoid accumulations (fig. 5). The included lymph nodes were not involved. The pathologic diagnosis was papillary adenocarcinoma of the parotid gland. The patient was discharged from the hospital and made an uneventful recovery.

CASE 4.—C. A., an 18 year old white youth, entered the hospital (T. M. J.) complaining of a tender swelling behind the left ear. He stated that it had become

progressively larger for the three years prior to admission but that tenderness had developed only during the past several months. It was recognized as a mixed tumor of the parotid gland and was resected. It weighed 2.5 Gm. Microscopic sections revealed a variable histologic structure consisting of dense, fibrous connective tissue with collagen bundles, lymphoid tissue and epithelial aggrega-



Fig. 5 (case 3, group 1).—Photomicrograph illustrating the papillary character of the tumor, with the delicate stroma free from lymph node accumulation.

tions. There were many areas of infiltration of plasma cells, lymphocytes, monocytes and polymorphonuclear neutrophils. The epithelial cells were in multiple layers, having the formation of squamous epithelium (fig. 6). There was no involvement of the lymph nodes. The pathologic diagnosis was benign squamous cell tumor of the left parotid gland (Dr. Thomas D. Robertson). The patient has recently (seven months later) returned with a recurrence.

*Comment.*—A summary of the essential data (table 1) in the 4 cases discloses that all the patients were men. From this group the tumors appear to be most common in the fourth decade of life, although they may occur at an earlier or a later age (1 patient was 18 and another 68). The tumors were all located in the region of the parotid gland. All of



Fig. 6 (case 4, group 1).—Photomicrograph showing the marked squamous cell character of the neoplasia.

them were of considerable duration, usually several years. Their clinical manifestations simulated those of the "mixed tumors," and they were so designated. Most of them were soft, fluctuant and partially cystic. As has been pointed out by McFarland, a certain "ripening" must obtain in the so-called mixed tumors before successful and complete surgical

removal is effected. This so-called "ripening" is probably nothing more than acquisition by the tumor of sharp definition and encapsulation, which also develop in these more uncommon tumors. The embryonic character of the epithelium indicates that it originates in either the respiratory tract or in the pharynx. The outstanding histologic feature is not only the papillary arrangement but the stroma, which is delicate and in some cases packed with lymphocytes showing numerous large germinal centers but without lymph sinus arrangement. Mitoses are, as a rule, absent. Warthin (previously mentioned) observed 2 instances (of lesions like those in cases 1 and 2) and commented on 2 others, previously recorded.

TABLE 1.—*Unusual Tumors of Salivary Gland Origin*

Case and Sex, Patient	Age	Site	Duration	Size	Clinical Diagnosis	Pathologic Diagnosis	Comment
Case 1 C. G. V.	M 68	Below angle of left jaw	Several years	"Small hen egg"	Mixed tumor of parotid	1. Benign cystic papilloma, branchial cleft 2. Papillary cystadenoma lymphomatosum	Returned with small recurrent tumor; removed; no recurrence
Case 2 J. M. N.	M 40	Below left ear, posterior to angle of jaw	3 years	"Small hen egg" (5 × 4 × 2 cm.)	Cystic tumor of jaw; malignant (?)	Papillary cystadenoma lymphomatosum	No recurrence
Case 3 P. O.	M 42	Cyst on left side of face	Unknown	1st removal: 2.5 × 2 × 1.2 cm.; 2d removal: 8 × 5 × 3 cm.	Recurrent mixed tumor of the parotid	Low grade papillary adenocarcinoma of parotid	Given 550,000 r units after 1st operation; no recurrence
Case 4 C. A.	M 18	Behind left ear	3 years	1 cm.; 2.5 Gm.	Mixed tumor of parotid; hard nodule, freely movable	Benign squamous cell tumor of the parotid	Radical treatment recommended in spite of benign appearance

He concluded that these neoplasias represent a heterotopia of mucous membrane from the pharyngeal entoderm of respiratory or eustachian tube anlagen, forming unusual and rare teratoids of the parotid region. Freshman and Kurland<sup>2b</sup> in a recent study were able to find 54 such neoplasms in the literature. These authors concluded that these lesions arise from the branchial pouches and often have a resemblance to either thymic cells or the acidophilic cells of the parathyroid gland. Variations of these tumors without the characteristic lymphoid structure and definite carcinoma formation undoubtedly occur, with some modification of type and location, depending on the particular "pouch" from which they originate.

2b. Freshman, A. W., and Kurland, S. K.: Cystadenoma Lymphomatosum. *Am. J. Clin. Path.* 8:422 (July) 1938.

## GROUP 2: UNUSUAL TUMORS OF BRANCHIAL CLEFT ORIGIN

While persistent branchial cysts or clefts are relatively common clinical entities, the malignant tumors that arise in them are not so frequent. We were surprised to find in our entire collection only 3 authentic instances of primary carcinoma in such embryonic formations.

CASE 1.—S. S. R., a 56 year old white man, complained of a slowly growing pea-sized swelling in the right submaxillary region, of one year's duration, and a second lump (near the first one), two months old. The patient had received anti-syphilitic treatment, and he thought that the last lump had appeared about the time



Fig. 7 (case 1, group 2).—Photograph illustrating the appearance and location of primary branchiogenic carcinoma.

of the last inoculation. The mass was sore to the touch and painful, and it limited motion of the lower jaw. It seemed to lie below the sternocleidomastoid muscle and was "fixed to the mandible and skin." Two roentgen treatments were given at different times. At operation (Feb. 3, 1933) a forceps was first inserted carefully into the depths of the mass, and chunks of cheesy, odorless material were scoped out digitally. A cavity could be felt extending anteriorly and posteriorly for 2 inches (5 cm.). The opening to this cavity was dilated, and the entire cavity was gently curetted and then packed with iodoform gauze. A small portion of skin and subcutaneous tissue in the region of the incision was sent to the pathologist with the tentative clinical diagnosis of actinomycosis of the neck (fig. 7). Microscopically, sections revealed some epidermis, which suddenly gave way to an extensive cellular mass which deeply infiltrated and largely replaced the corium.



A part of the surface epithelium and also the neoplasm had undergone necrosis and showed secondary infection. Epithelial pearl formation was in evidence. Deep in the tumor there were areas of suppuration, hemorrhage and large clumps of bacteria. The pathologic diagnosis was branchiogenic epithelioma of the neck with necrosis and secondary infection (Dr. Warren C. Hunter). The patient died, and postmortem examination was not permitted.

CASE 2.—H. H. R., a woman aged 69, complained of a slowly growing, painless mass of two years' duration, unattached to the skin or to the deep tissues and

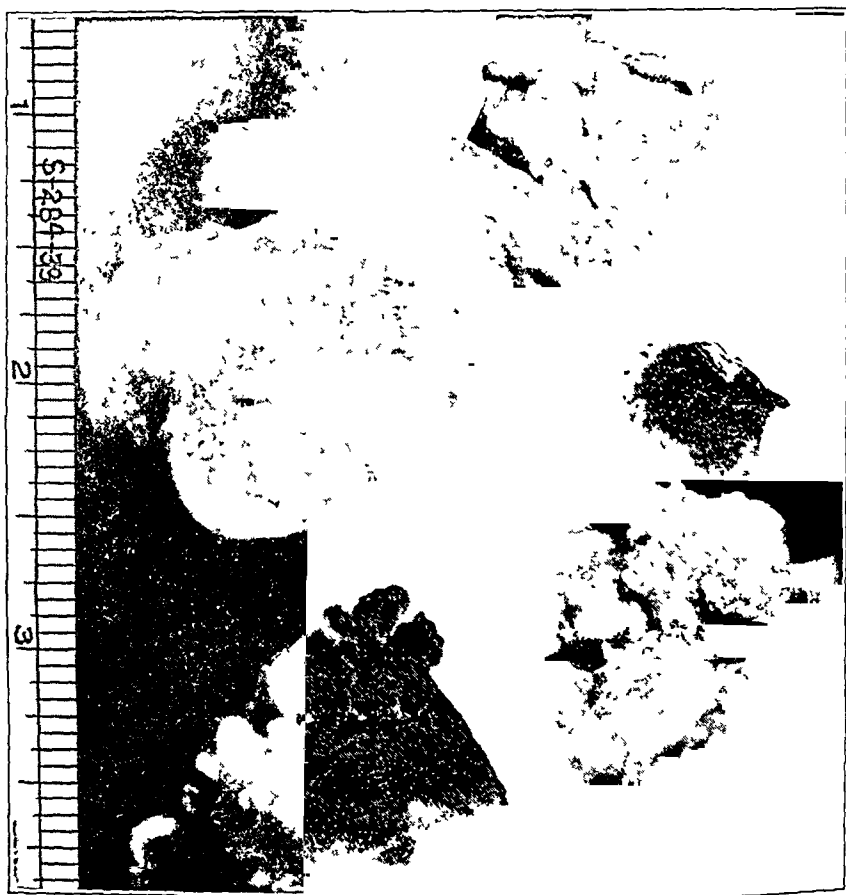


Fig. 8 (case 2, group 2)—Photograph of the branchial cleft tumor, showing its soft, lobulated character.

located in the left upper cervical region. After operative removal the tumor (3.5 cm. in diameter) was found to be encapsulated but torn, some of its contents being exposed. It consisted of multiple soft masses separated by sinusoid-like spaces with smooth white surfaces. The tissue was very soft and was homogeneous in appearance (fig. 8). Microscopically, a definite pseudostratified columnar epithelial structure (respiratory type) was observed. The cells occurred in masses or atypical papillary formations, with central necrosis accounting for the cyst formations. The stroma was largely lymphoid, without germinal follicles and with well defined vascularity. The pathologic diagnosis was benign adenomatoid hyperplasia of branchial cleft origin (W. C. H.).

CASE 3.—S. K., a 45 year old woman, entered the hospital on Jan. 2, 1932, complaining of a swelling of the right side of the neck, with difficulty in swallowing. Ten months previously she had noted a small, painless lump 2 inches (5 cm.) below the mandible. It had gradually increased in size, and during the last three months the patient had begun to expectorate pus, which she felt came from the neck. This progressed to fulness under the chin with a soft swelling of the right side, which ruptured and drained one month before admission. Later, a firm, fungoid, painless vascular swelling of the palate and the right lateral pharyngeal wall appeared, with a corresponding dusky, firm swelling (3 by 4 by 3 inches) on the right side of the neck, below and anterior to the angle of the jaw. Diagnoses of carcinoma of the tonsil or soft palate, mixed tumor of the parotid gland, tuberculous adenitis and actinomycosis were considered. Biopsy of material from the pharynx revealed epidermoid carcinoma with secondary infection. Ten

TABLE 2.—Unusual Tumors of Branchial Cleft Origin

Case and Sex, Patient	Age	Site	Duration	Size and Type	Clinical Diagnosis	Pathologic Diagnosis	Comment
Case 1 S. S. R.	M 36	Posterior cervical triangle, about middle of sterno- cleidomastoid muscle	1 year	About 3 × 3 / 2.5 cm.	Actinomy- cosis	Branchiogenic carcinoma with secon- dary infection and necrosis	Patient given roentgen therapy; died
Case 2 H. H. R.	F 69	Left infra- auricular region	2 years	Encapsulated cystic mass 6 × 3.5 × 2.5 cm.	Tumor of the neck	Branchial cyst with hyperplasia of respiratory and pharyn- geal types of epithelium	Histologic structure similar to that in case 1, group I
Case 3 S. K.	F 45	Lump right side of neck 2 inches (5 cm.) below mandible	10 months	Pedunculated dusky swell- ing 3 × 3 × 4 inches (7.6 × 7.6 × 10 cm.)	Carcinoma of tonsil or soft palate; mixed tumor of parotid; adenitis; actinomycosis	Squamous cell carci- noma, prob- ably bran- chiogenic	Patient died 10 days after admission; autopsy confirmed diagnosis

days after admission the patient died. The pertinent anatomic observations at autopsy were as follows: primary branchiogenic carcinoma of the neck with extensive involvement of the base of the tongue, pharynx and right tonsil (grade IV); marked secondary infection; compression of the trachea, and purulent tracheobronchitis.

*Comment.*—It will be noted, as is generally true, that these tumors (table 2) occur after the fortieth year (Ewing<sup>3</sup>). The most common site is the upper part of the neck (infra-auricular) region. In the instances reported here the growths were of relatively short duration (ten months to two years). They were not unusually large and showed a marked tendency to be globular, ramifying cystic formations with secondary infection and induration, giving the impression of a chronic granulomatous process. One of them was confused with actinocycosis and was

3. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

treated accordingly. Another (case 3) was a progressive, massive tumor with a distribution highly suggestive of so-called primary lymphoepithelioma. The other (case 2) had a cellular pattern not unlike that of the unusual tumors of salivary gland origin and was considered wholly benign. It is evident from this small group that recognition of primary branchiogenic tumors is often difficult, since they may simulate many other epidermoid carcinomas of primary or secondary origin in the cervical region. The presence of a ramifying infected sinus or of multiple cysts with cheesy content; late involvement of lymph nodes by carcinoma; early extension to nodes in infections, and elimination of other primary sources are all diagnostically important. The spreading, sinusoid character of these lesions makes their removal difficult and their prognosis grave. It is possible that these tumors are of frequent occurrence but are seen late, when they become indistinguishable from other epidermoid carcinomas, particularly "lymphoepithelioma." The per cent of branchiogenic cysts which become malignant is not known.

#### GROUP 3: UNUSUAL TUMORS OF THYROID AND PARATHYROID ORIGIN

Hypertrophic or nodular metastases, physiologic, inflammatory, pseudoneoplastic or neoplastic, in the thyroid gland are in themselves sufficiently complicated to tax the ingenuity of both the clinician and the pathologist. In addition to such more usual manifestations, there are growths of congenital origin, such as cysts of the thyroglossal duct, sublingual aberrant thyroids and the substernal aberrant thyroids that are generally recognized and occasionally observed. The thyroid gland, in addition to these more common pathologic changes, is the site of some unusual intrinsic tumors that may give rise to local and occasionally to distant disseminations of a peculiar type. In addition (because of the close association with the anlage of the thyroid gland), some well recognized tumors of the parathyroid may confuse the diagnosis. Accordingly, we have grouped several of these neoplasias because of their oddity and infrequent occurrence.

CASE 1.—J. I. M., a woman aged 59, was admitted to the hospital on March 2, 1940, complaining of nervousness, tremor, loss of weight, a mass in the neck, palpitation and an afternoon fever (temperature, 100 to 102 F.). She stated that six years previously she had been told that she had a toxic goiter, but the symptoms had become severe only one month before admission. Examination disclosed a nodular enlargement of the left lobe of the thyroid. The pulse rate never exceeded 84. Operation (Drs. W. B. Holden and E. E. Rippey) yielded a thyroid gland weighing 80 Gm. One entire lobe was found to contain a soft encapsulated nodule. The remaining portion revealed a firm, white to yellow, almost cartilaginous-appearing structure which obliterated the normal thyroid parenchyma. Histologically, in this area there was observed a great reduction in the alveoli and extensive fibrosis, with a vast quantity of intercellular collagen. There was

also marked lymphocytic infiltration, with well formed germinal centers. It was pointed out that this gland could be diffusely hyperplastic, with regression occurring spontaneously or under the influence of iodine. However, the marked inflammatory picture led to the diagnosis of Riedel's struma (woody or phlegmonous thyroid) together with solitary adenoma.



Fig. 9 (case 4, group 3).—Photomicrograph illustrating branching thyroid epithelium in a cervical lymph node.

CASE 2.—T. B., a 72 year old woman, entered the hospital on Jan. 16, 1939, with difficulty in breathing and swallowing and palpitation of the heart. She stated that about six months prior to admission she had noted profuse sweating together with a rapid heart and fulness of the neck. The symptoms became more pronounced about two months prior to her admission. It was noted that there was an asymmetric bilateral enlargement of the thyroid, which was firm but not

tender, with deviation of the trachea to the right. The condition was regarded as a diffuse toxic goiter with low grade hypertension. The removed gland weighed 340 Gm. The surfaces made by sectioning were large and white. The central portion of the cellular areas was soft and vascular. In other places there was spotting with brownish gray areas of obviously colloid-containing lobules.

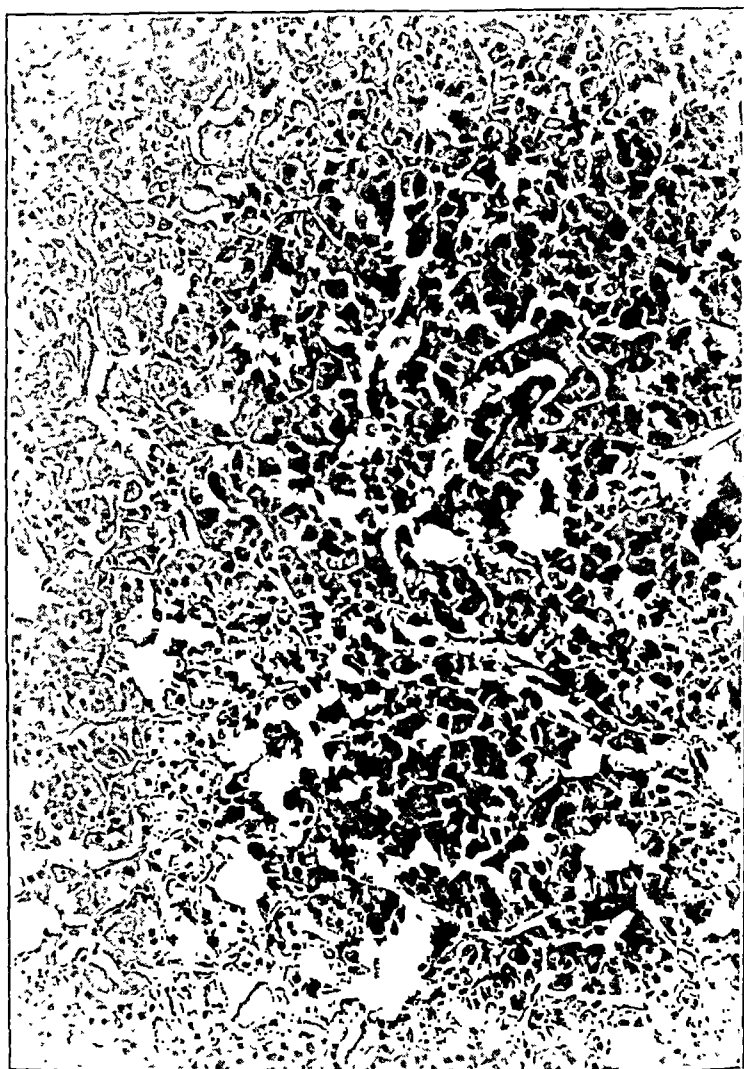


Fig. 10 (case 7, group 3).—Photomicrograph of a Hürthle cell carcinoma of the thyroid.

Histologically, there was observed an abundance of lymphoid tissue with numerous germinal centers. The remaining thyroid acini were distinctly inactive rather than hyperplastic. The abundance of lymphoid tissue was strongly suggestive of lymphosarcoma; however, the fibrosis associated with the lymphoid distribution indicated a hyperplastic thyroid gland which had apparently "burned out." The pathologic diagnosis was massive lymphoid hyperplasia of the thyroid gland, so-called lymphadenoma or Hashimoto's disease.

CASE 3.—R. J., a 5 year old boy, entered the hospital on May 28, 1936, with a cyst of the neck. The mass was first noted when the child was  $1\frac{1}{2}$  years old. It was drained several times and excised, but recurred. The clinical diagnosis of thyroglossal cyst was made, and operative removal followed. Recovery was uneventful, with no recurrence. Pathologic examination (W. C. II.) disclosed an infected thyroglossal cyst with a heterotopic thyroid.

CASE 4.—B. J., a 19 year old youth, entered the hospital on Feb. 2, 1939, with a small, hard lump in the right side of his neck that had been present for years but had increased in size during the previous year. The lymph node was removed, and a diagnosis of probable so-called Hurthle cell carcinoma of the thyroid gland

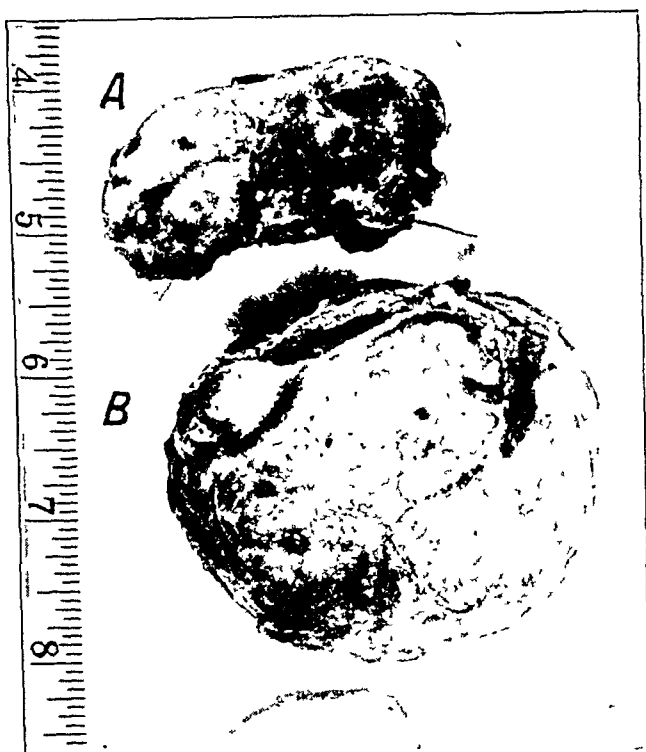


Fig. 11 (case 7, group 3).—Photograph of the nodular hyperplasia of the right lobe (A), and the larger, Hurthle cell carcinoma (B).

with metastases to the cervical glands was made (fig. 9). No other evidences of spread were observed clinically. On the basis of the aforementioned diagnosis the patient was given 4,500 milligram hours of radium, and the dose was repeated three months later. About three months later, two lymph glands of the neck were excised, with a diagnosis of probable metastatic carcinoma of the thyroid gland. Later the patient appeared at the tumor clinic, and at present he has had no recurrences and is apparently well.

CASE 5.—D. Y., a man 23 years of age, entered the hospital complaining of a tumor of the neck about 1 inch (2.5 cm.) from the median line. He stated that it bothered him in swallowing and that he had first noticed it ten years prior to admission, but he sought medical advice because it had been growing noticeably in the previous two months. It was observed that the tumor of the neck was

about 1 inch lateral to the thyroid cartilage. It was movable and not sensitive and was the size of a walnut. It was removed, the patient making an uneventful recovery. Pathologic examination disclosed a definite rounded nodule with a fibrous connective tissue capsule. It was yellowish and translucent and in certain areas had a reddish brown hue. Fibrous connective tissue, a few accumulations of lymphocytes and papillary projections were present. It was recognized as an aberrant papilloma of the thyroid. It has not recurred.

CASE 6.—A woman aged 65 came to the hospital complaining of a mass in her neck. She stated that six months prior to this time she had been operated



Fig. 12 (case 7, group 3).—Photograph of the surfaces made by sectioning the Hürthle cell tumor.

on for goiter. About one month before admission the neck began to swell, and there were dyspnea, cough and cyanosis and fever. Roentgen examination disclosed many discrete rounded areas in the chest. The patient died two weeks after leaving the hospital. Autopsy was not performed. A section of the tumor was submitted to one of us (F. R. M.) for examination. This disclosed a tumor with very large polyhedral acidophilic cells with many mitotic figures; it was recognized as a carcinoma of the thyroid, of the Hürthle cell type.

CASE 7.—W. D., a 68 year old white woman, was admitted to the hospital on March 18, 1939, complaining of difficulty in breathing lasting a few minutes, occurring at night and associated with palpitation. She stated that she had had

TABLE 3.—Unusual Tumors of Thyroid and Parathyroid Origin

Case and Patient	Sex, Age	Site	Duration	Size	Clinical Diagnosis	Pathologic Diagnosis	Comment
Case 1 J. I. M.	F 59	Nodule in thyroid gland	6 years	1st: $8\frac{1}{2} \times 5 \times 3.5$ cm.; 2d: $7 \times 4.5 \times 2.5$ cm.	Toxic goiter	Riedel's struma; also, solitary adenoma of the thyroid	No connection between adenoma and Riedel's struma; recovery
Case 2 T. B.	F 72	Region of thyroid gland	1 year	340 Gm.; $10 \times 8 \times 8$ cm.; $9 \times 6 \times 4.5$ cm.; $5.5 \times 3 \times 1.5$ cm.	Diffuse toxic goiter	Chronic thyroiditis (Hashimoto's disease)	Recovery
Case 3 R. J.	M 5	Cyst in region of thyroid gland	3½ years	About 1 cm. in diameter	Thyroglossal cyst	Thyroglossal cyst and heterotopic thyroid	Heterotopic thyroid found lateral to thyroglossal cyst
Case 4 B. J.	M 19	Right side of neck	Years (?); has grown considerably in the past year	$4 \times 2 \times 2$ cm.; $2 \times 1 \times 0.5$ cm.	Carcinoma of the thyroid	Heterotopic thyroid	First diagnosis: adenocarcinoma; roentgen therapy following operation; recovery
Case 5 D. Y.	M 23	About 1 inch (2.5 cm.) from the mid-line to left of thyroid cartilage	10 years	$1.5 \times 2 \times 1$ cm.	Tumor of the neck	Heterotopic thyroid with papilloma formation	Recovery
Case 6 F 65	F 65	Mass in region of thyroid	6 months (?)	Unknown	Goiter	Hürthle cell carcinoma	Metastases in lungs; expired 2 weeks after discharge from hospital; no autopsy
Case 7 W. D.	F 68	Left side of neck	20 years	$6.5 \times 3 \times 4$ cm.; 8 cm. in diameter	Nodular nontoxic goiter	Nodular adenomatous hyperplasia of thyroid, right; Hürthle cell tumor, left	Recovery
Case 8 M. L.	F 69	Both sides of neck	7 years (treated by chiropractor)	About size of grapefruit on left and of baseball on right	Hodgkin's disease or lymphosarcoma	Papillary carcinoma of the thyroid	Autopsy reveals characteristic distribution of carcinoma of the thyroid
Case 9 J. E. W.	F 27	Isthmus of thyroid	About 2 years	5 cm. in diameter; circular	Toxic adenoma of the thyroid	Liposarcoma (?)	Recovery
Case 10 H. S.	M 42	Left side of the neck; mass not palpable; diffuse	1½ years (blood calcium, 11.1 mg., and cholesterol, 152 mg. per 100 cc.)	$2 \times 1 \times 0.5$ cm.; $1 \times 0.6 \times 0.5$ cm. (calcium-phosphorus ratio, 3.66 : 1)	Parathyroid tumor	Diffuse infiltrating adenoma of the parathyroid	Marked clinical improvement; recovery
Case 11 B. C.	M 56	Left side of neck, overlying external and internal carotid arteries	5 to 6 years	$11 \times 8 \times 6$ cm.	Carotid body tumor	Adenoma of the parathyroid	Died on 5th postoperative day; no autopsy



a swelling on the left side of the neck for the last twenty years. She noted a recent 20 pound (9 Kg.) loss in weight, associated with nervousness and frontal headaches. She had had several previous operations. Her blood pressure was 165 systolic and 80 diastolic; her pulse rate was 96. Examination disclosed a soft, movable mass in the thyroid, just underneath the sternocleidomastoid muscle, the

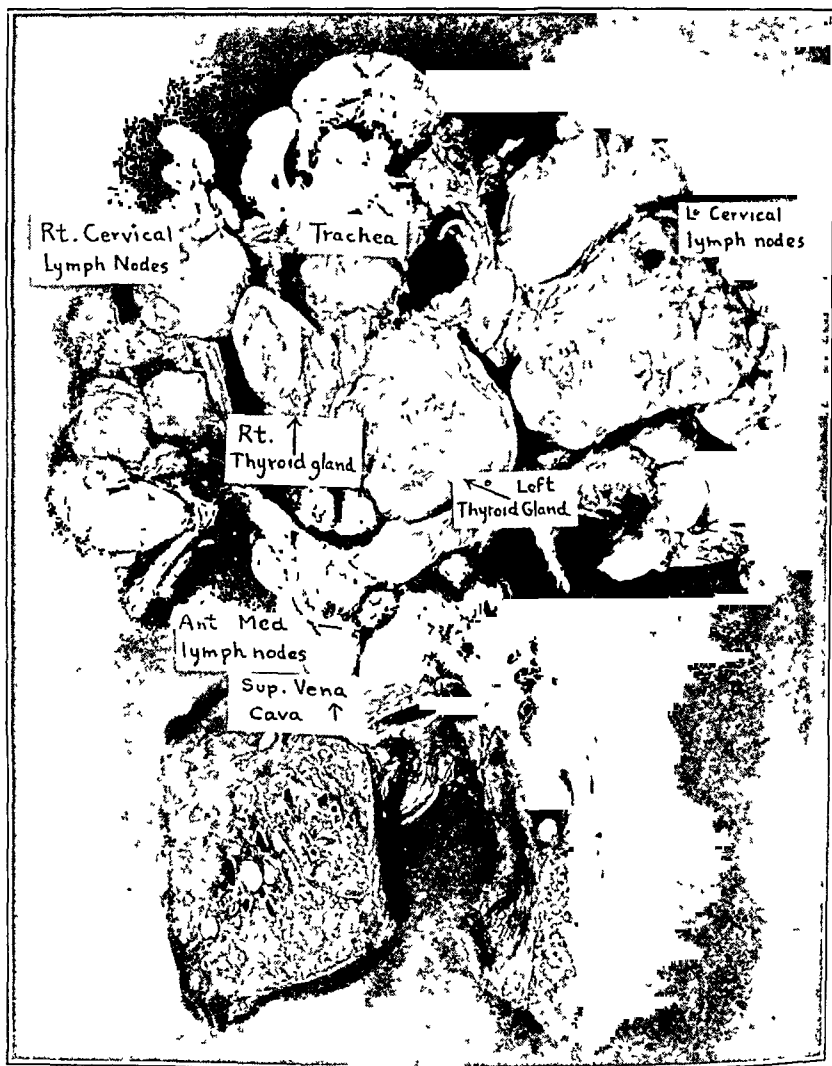


Fig. 13 (case 8, group 3).—Photograph of a papillary carcinoma primary in the thyroid. Note the massive local and lateral spreads as compared with the small number of nodules seen metastatically in the lungs (anterior view).

size of a baseball. At the lower pole of the left lobe there was a nodule measuring 6.5 by 3 by 4 cm. The right lobe measured 8 cm, was somewhat cystic and was grayish white to pinkish red and firm. It was partially hemorrhagic. The final diagnosis was nodular adenomatous hyperplasia of the thyroid, with a Hurthle cell tumor in the left lobe (figs. 10, 11 and 12). Recovery was complete, and there has been no recurrence up to the present.

CASE 8—M. L., a 69 year old woman, was admitted to the hospital complaining of a growth in the right side of the neck that had been present for seven years. The enlargement had been gradual. She received treatment from a chiropractor, after which she stated that the mass diminished in size. During this time, however, lumps developed on the left side of the neck, and both sides



Fig. 14 (case 8, group 3) —Papillary carcinoma of the thyroid (posterior view), showing deviation of the trachea, encasement of blood vessels and the descent into the mediastinum

gradually enlarged. There finally developed a choking sensation, and a portion of the gland was removed for biopsy. Physical examination disclosed bilateral nodular enlargement composed of more or less discrete glands in the upper cervical region, with glands matted together in the lower part of the neck. The skin was freely movable over them. The extreme nodularity led to the clinical con-

clusion that the patient was suffering from Hodgkin's disease, a lymphosarcoma or some other malignant growth. She appeared at the tumor clinic one month after her first appearance and at this time consented to a biopsy, which disclosed the presence of a papillary carcinoma. She stated that a previous biopsy had disclosed a squamous cell carcinoma. Her condition became progressively worse,

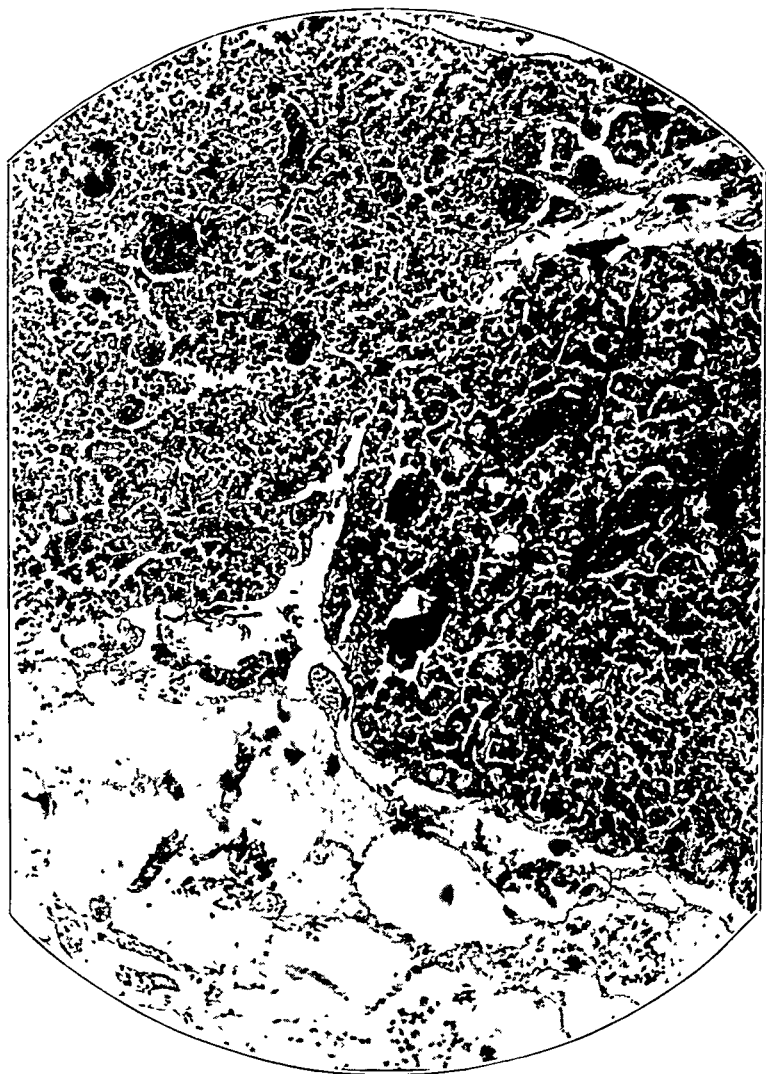


Fig. 15 (case 8, group 3).—Photomicrograph illustrating a metastatic nodule in the lung (primary carcinoma of the thyroid). Note the tendency toward a hyperactive, functional structure.

and she died five months after first being seen. During this interval she had had some high voltage roentgen therapy. At postmortem examination an extensive primary papillary carcinoma, adenocarcinoma of the thyroid with aberrant lateral invasions, massive involvement of all cervical lymph nodes and an extension downward into the mediastinum, with multiple metastases to the lungs, was observed (figs. 13, 14 and 15).

CASE 9.—J. E. W., a woman 27 years of age, weighing 226 pounds (102.5 Kg.), was admitted to the hospital on Nov. 4, 1939, complaining of nervousness and menstrual difficulties. Her basal metabolic rate was +30 per cent, and she was thought to have a toxic adenoma. She was given compound solution of iodine U. S. P., and the nodule was later removed. Pathologic examination showed an

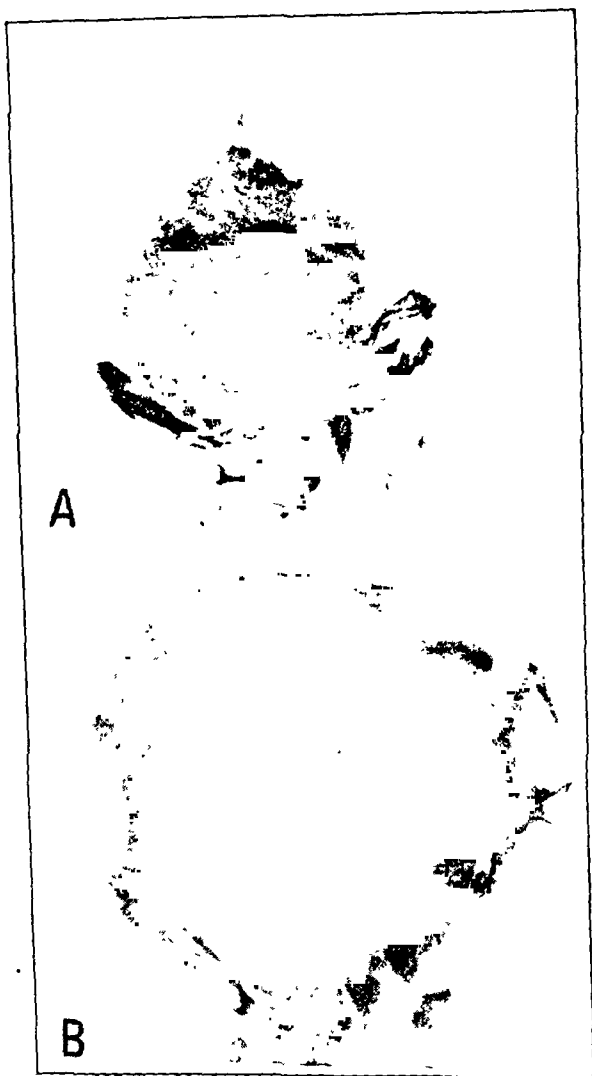


Fig. 16 (case 10, group 3).—*A*, reproduction of the roentgenogram of the skull prior to removal of the parathyroid hyperplasia. *B*, roentgenogram showing the marked filling in of defects after the removal of the parathyroid tumor. Compare with *A*.

encapsulated cellular mass 5 cm. in diameter. The surfaces made by sectioning revealed a yellowish brown, soft, somewhat friable tumor having the consistency of well fixed brain, with small cystic areas filled with a clear fluid. In the center of the tumor there was a definite zone of hyaline scar tissue similar to that

commonly seen in solitary adenomas. Microscopic examination disclosed marked general vascularity with rather extensive hemorrhages. The connective tissue stroma varied considerably. In some places it was delicate, and in other places it expanded into bands. The entire tumor was definitely cellular, with uniformity in appearance of the cells, a basophilic, often vacuolated, cytoplasm and spindle-



Fig. 17 (case 10, group 3).—Photomicrograph illustrating the diffuse hyperplasia of parathyroid tissue into the adjacent fat.

shaped or round nuclei. Occasional somewhat atypical mitotic figures could be seen. Fat stains of the tumor mass disclosed an abundance of lipoid material thickly studding all of the cells. The pathologic diagnosis was liposarcoma developing in an adenoma of the thyroid.

CASE 10.—H. S., a 41 year old man, entered the hospital on April 12, 1937, complaining of pain behind his left ear. He stated that he had been well until

one and a half years before admission, when he had noticed occipital headache starting behind the left ear and extending down into the neck. Liquor aggravated it. He began feeling depressed and felt dull and heavy. He did not appear acutely ill. He had normal muscle tone and was well nourished. There was pain on light pressure over the left side of the skull. Roentgen studies of the skull revealed multiple areas of diminished density (fig. 16 *A*). Another, similar area of decreased density was noted in the left clavicle. The value for blood calcium was 11.1 mg. and that for cholesterol 152 mg. per hundred cubic centimeters. There was a calcium-phosphorus ratio of 3.66:1. Operation for parathyroid tumor was carried out. No tumor mass was found, but in the region of the right lower



Fig. 18 (case 11, group 3).—Photograph illustrating the massive unilateral tumor of the parathyroid.

lobe, posteriorly, there was found a "small, firm, yellowish, cordlike mass about 2 cm. long." Another mass of fatty tissue, about 1.0 cm. across, was found attached to the capsule. Frozen sections made at the time of operation failed to show any other tissue but that having the typical chicken wire appearance of fat. After the paraffin sections were made, there was found infiltrating the fat a definite so-called *Wasserhelle* cell (clear cell) diffuse infiltrating adenoma of the parathyroid (fig. 17). After surgical removal of the growth the headaches disappeared, and subsequent roentgenograms of the skull and of the clavicle revealed regression of the rarefaction process (fig. 16 *B*). At present the patient is feeling perfectly well.

CASE 11.—B. C., a 56 year old man, was admitted to the hospital on Feb. 8, 1937, complaining of a tumor of the left side of the neck. It was roughly spherical, measuring 5 to 6 cm. in diameter, and was freely movable and solid. The blood pressure was 140 systolic and 80 diastolic. At operation (local anesthesia) a tumor overlying the internal and external carotid arteries, intimately attached to the jugular vein (removed) and having a questionable attachment to

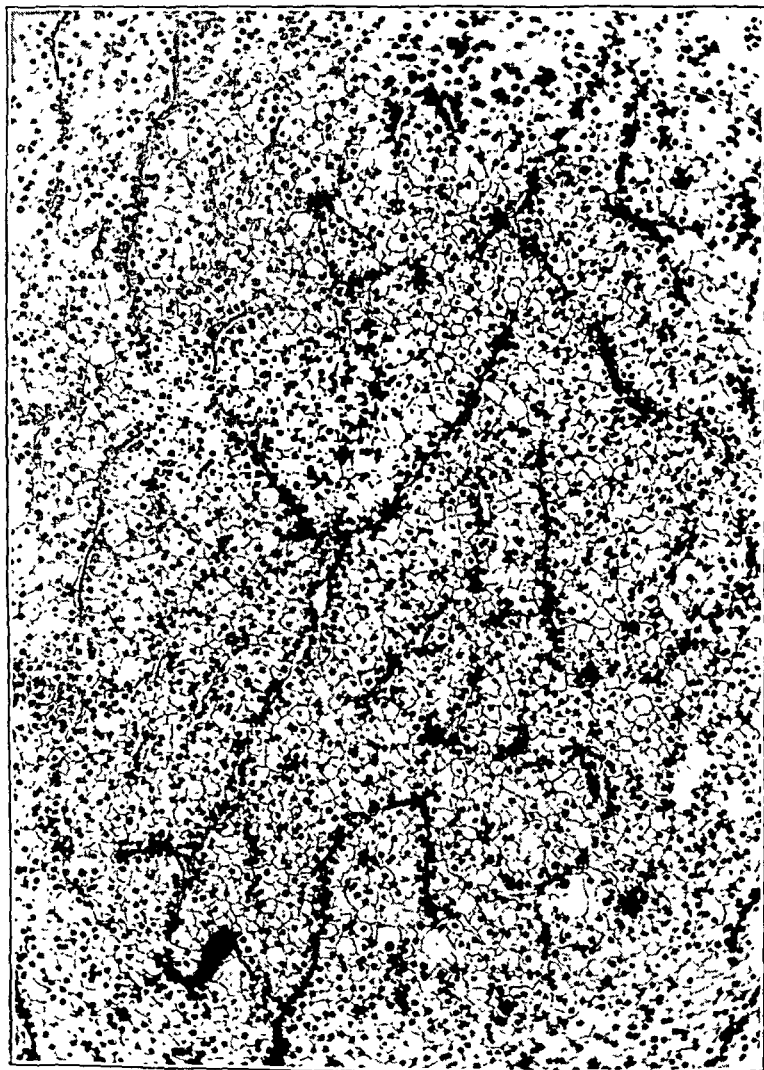


Fig. 19 (case 11, group 3).—Photomicrograph illustrating the microscopic appearance and the compact character of the new growth.

the parotid gland was removed. The postoperative condition was poor. Cyanosis developed; this was followed by coma, and he died a day later from acute edema of the larynx. On pathologic examination, the specimen measured 11 by 8 by 6 cm. The surfaces made by sectioning were moist and partly pale but studded with tiny hemorrhages. It had the gross appearance (fig. 18) of a firm but very edematous sarcoma (Dr. B. T. Terry). The microscopic section was found to reveal

the typical pattern (fig. 19) of a large and extensive parathyroid adenoma (F. R. M.). It is unfortunate that other detailed evidences in the history are lacking, since there was no complete examination, including roentgen and other investigations. The pathologist had regarded it as a probable so-called tumor of the carotid body.

*Comment.*—The instance of Riedel's struma is presented here for the purpose of contrasting the condition with Hashimoto's disease (case 2). Surgeons are sufficiently familiar with this very hard, pseudoinflammatory, "burned-out" type of gland, so ably discussed in the recent literature by Hellwig,<sup>4</sup> Jaffé<sup>5</sup> and others, who have regarded it as inflammatory but not necessarily infectious. It is often questionable whether a true inflammation exists or whether the process is simply a profound hyperactivity that spends itself and excites lymphocytic and connective tissue replacement. At any rate, it is noteworthy that in such specific or borderline instances myxedema may follow radical removal, because what little gland is left behind is similarly obliterated. The instance of Hashimoto's disease, in which the tissue was so strikingly pervaded by lymphocytes to the exclusion of most of the acinar structure, raised the question whether a true lymphosarcoma was really present. Joll's<sup>6</sup> masterful review lists some twenty-odd different terms that are applied to such modifications of the thyroid gland. Many investigators regard Riedel's struma and Hashimoto's disease as different stages of the same entity. Joll, however, stated that the characteristic histologic changes of Hashimoto's disease are "a diffuse lymphocytic infiltration associated with the presence of germinal follicles with a wide-spread, though peculiar, destruction of thyroid parenchyma followed by fibrosis." The author apparently wished to point out that the lymphatic invasion is primary and that there are other marked clinical and pathologic differences between Riedel's struma and Hashimoto's disease. It must be remembered, however, that there is a marked tendency in all forms of goiter for eventual formation and accentuation of lymphoid follicles; so much so, that Warthin<sup>7</sup> referred to exophthalmic goiter as a lymphatic constitutional disease. It would not, therefore, be impossible for certain unusually and peculiarly violent forms of hyperthyroidism to develop maximum obliterating phenomena with heavy lymphoid accumulations, simulating tumors. It is also noteworthy that in both of these instances (cases 1 and 2) toxic hyperthyroidism existed. Accordingly, in spite of Joll's masterful paper, there is in it an element of a difference without a distinction.

4. Hellwig, C. A.: Lymphadenoid Goiter, *Arch. Path.* **25**:839 (June) 1938.

5. Jaffé, R. H.: Chronic Thyroiditis, *J. A. M. A.* **108**:105 (Jan. 9) 1937.

6. Joll, C. A.: The Pathology, Diagnosis, and Treatment of Hashimoto's Disease (Struma Lymphomatosum), *Brit. J. Surg.* **27**:351 (Oct.) 1939.

7. Warthin, A. S.: The Constitutional Entity of Exophthalmic Goiter and So-Called Toxic Adenoma, *Ann. Int. Med.* **2**:553, 1928.



The next 3 instances in this group represent abnormal distributions of thyroid gland structure. In 1 instance (case 3) thyroid residue was found in a thyroglossal cyst. This was undoubtedly a benign embryonic abnormality. In the other 2 instances it was found in the lymphatic glands. In both there were exhibited forms of papillary hyperplasia commonly associated with simular low grade benign tumors within the gland itself. Crile,<sup>8</sup> in a recent article, pointed to the frequent existence of such aberrant thyroid tumors in the adjacent tissues and lymph nodes of the neck. He mentioned that these are indistinguishable from papillary tumors of the thyroid. In 45 of 136 cases reported by him the growth was classified as malignant, but only 2 of the 45 patients died from recurrences. This author further pointed out that many tumors have been diagnosed as carcinoma of the thyroid which had no demonstrable metastases in the lymph nodes. He therefore considered the possible anomalous occurrence of these lesions and stated that all cervical sinuses, cysts and embryologic anomalies of the neck show a striking tendency to include lymphoid tissue and that benign aberrant thyroid tissue is no exception. While it is reasonably possible that such aberrant formations exist, it must be remembered that there is an intimate and very rich vascularity of the thyroid gland, which not infrequently permits escape of viable thyroid tissue through the capsule or into the veins and secondary implantation of such elements with subsequent secondary growth. Papillary formations within the thyroid gland are exceedingly common in all forms of goitrous enlargements. One frequently sees invasions of the veins by adenomas or adenomatous lesions of the thyroid. Simpson<sup>9</sup> recorded 3 instances of thyroid metastases to bones, discussed the existence of so-called "benign metastasizing goiter" and gave Cohnheim<sup>10</sup> the credit for first reporting simple colloid goiter with metastases. We also have observed a number of cases in which definitely normal-appearing thyroid tissue was found in bones. It was Simpson's conclusion that the belief of some writers that metastatic lesions actually represent aberrant thyroid tissue has no basis in fact. To support this contention, he further reported 2 instances in which there were osseous metastases from microscopically benign thyroid tissue, associated with clinically benign goiters. There was, however, later evidence of carcinomatous change in 1. Simpson finally concluded that so-called "benign metastasizing goiter" is a term that should be abandoned, there being no

8. Crile, G., Jr.: Tumors of Lateral Aberrant Thyroid Origin, *J. A. M. A.* **113**:1094 (Sept. 16) 1939.

9. Simpson, W. M.: Three Cases of Thyroid Metastasis to Bones, with a Discussion as to the Existence of the So-Called Benign Metastasizing Goiter, *Surg., Gynec. & Obst.* **42**:489 (April) 1926.

10. Cohnheim, J.: Einfacher Gallertkropf mit Metastasen, *Virchows Arch. f. path. Anat.* **68**:547, 1876.

entity of this particular kind. While it is true that one often observes metastatic thyroid nodules that in every way appear to be benign and functioning, such lesions must be regarded as not only aberrant but neoplastic. It is an established observation that many times the metastatic thyroid lesions appear as normal, functioning elements, while one may find within the thyroid gland itself distinctive carcinomatous changes. Evidence of such a condition is at hand in the instance (case 8, group 3, fig. 15) in which the metastases in the lungs showed definite evidence of a functioning structure. We are, therefore, of the opinion that there is a preponderance of evidence to support the contention that there is no such entity as histologically malignant and clinically benign thyroid infiltration, other than those well recognized congenital displacements or teratoid inclusions.

The next two unusual tumors (cases 6 and 7) are peculiar only because of the presence of varying degrees of so-called Hürthle<sup>11</sup> cell accumulations. These cells were originally described as large, with an abundant cytoplasm, distinguishable by their considerable size, by their finely granular appearance and by the large single nucleus. Their cytoplasm is somewhat acidophilic. Hürthle considered them extracellular structures, probably of posterior branchial cleft origin. In many instances of thyroid hyperplasia small groups of similar cells can be seen. Occasionally they develop into distinctive carcinoma, maintaining the characteristic Hürthle cell type (case 7).

Case 8 is an instance of papillary carcinoma of the thyroid that was confused with Hodgkin's disease and lymphosarcoma. It aptly illustrates the slow and progressive invasion of cervical tissue and lymph nodes. It is unnecessary to point out the maximum concentration of the malignant neoplasia in the cervical region laterally, in contrast with the scattered dissemination down into the lung.

One instance of an unusual, deceiving tumor (case 9) having the appearance of a definite adenoma with toxicity caused considerable surprise because of its richly cellular pattern, indicating a possible mesoblastic origin. The abundance of fat together with the cytologic formations led us to the conclusion that this was probably a liposarcoma arising in an old adenoma. Ewing stated the opinion that many of these so-called sarcomas are in reality carcinomas with spindling of the epithelial cells. Yet one cannot hold that sarcomas of the thyroid never occur. The pathologic diagnosis in this case was made after detailed study and also in the light of the normal existence of fat in thyroid epithelium.

11. Hürthle, K.: Beiträge zur Kenntnis des Secretionsvorgangs in der Schilddrüse, Arch. f. d. ges. Physiol **56**:1, 1894.

The last 2 cases in this group are instances of definite parathyroid tumors. One (case 10) is of particular interest because of the extensive demineralization of bones and the marked clinical manifestations occurring in sharp contrast with the scant evidence of tumor. The fact that this diffuse parathyroid adenoma was responsible for the excess secretion of parathormone is beautifully illustrated by the immediate initiation of recovery and reversal of the osseous process that followed its removal. For a consideration of this problem of hyperthyroidism, the reader is referred to the article by Castleman and Mallory.<sup>12</sup> These authors concluded that the pathologic observations in the parathyroid gland are sharply divided into two types, hyperplasia and neoplasia, with the cells of either the "water-clear" or rare granular type. The 2 instances reported here confirm this concept.

#### GROUP 4: TUMORS OF MISCELLANEOUS ORIGIN

CASE 1.—J. M., a 65 year old man, entered the hospital with a small lump under the chin that had developed two years previously. It was removed but recurred and became progressively larger. Examination revealed a large, firm, rounded mass below the mandible in the midline, not adherent to the underlying structure. It was regarded as a cyst of the thyroglossal duct or a degenerating lipoma (T. M. J.) and was removed. The pathologist reported a liposarcoma of the neck. Radium (5,360 milligram hours from Jan. 8 to 11, 1935) and 3,216 milligram hours (June 5) was applied postoperatively. The patient returned about a year later (Nov. 30, 1936), with another lump which was removed, with further resection of lumps and glands on the following dates: Dec. 1, 1936; Aug. 16, 1937; March 14, Aug. 11 and Dec. 13, 1938, and Aug. 22 and Dec. 4, 1939, with final cessation of recurrences. Roentgen therapy was used as an adjunct.

CASE 2.—F. C. S., a 59 year old woman, entered the hospital on July 8, 1934, with a large mass on the left side of the neck that had been present for about twenty-nine years. She had first noticed it after a slight trauma. It was slightly tender to pressure. A month previously the large blood vessels surrounding the mass had been ligated. Examination disclosed a large, firm mass extending from under the ear almost to the clavicle. A loud bruit was heard. Resection of the tumor was performed on July 10. The specimen weighed 44 Gm. and measured 6 by 4.5 by 3.5 cm. The major part of the external surface was roughened by fibrous and fatty tags. There was a portion of artery coursing longitudinally through the specimen. On section an encapsulated and mildly lobulated tumor was found. At one edge of the section, through the middle, was an empty cavernous space with a smooth gray inner lining. The tissue supporting this plexus-like group of veins with the larger cavernous space appeared grayish and fibrous, cutting with fibrous resistance. The periphery of the tumor (of all but the area just described) was composed of glistening brownish yellow tissue. Microscopically, the more fibrous end and the vascular portion of the tumor showed broad, interlacing strands of collagen-containing connective tissue, throughout which were numerous vascular channels. These were lined by a single layer

12. Castleman, B., and Mallory, T. B.: The Pathology of the Parathyroid Gland in Hyperthyroidism: A Study of Twenty-Five Cases, *Am. J. Path.* 11:1 (Jan.) 1935.

of flattened endothelial cells with no muscularis. In this more fibrous area there were clusters of elongated to polyhedral cells lying adjacent to capillaries, which were in turn lined by a single layer of flattened endothelial cells. The pathologic diagnosis (T. D. R.) was tumor of the left carotid body (perithelioma, Ewing's classification).

CASE 3.—S. C., a 55 year old woman, was admitted to the hospital on Aug. 3, 1939, with a blood pressure of 198 systolic and 100 diastolic, a pulse rate of 100 and a painful mass in the left side of the neck of six to seven years' duration. She was treated with high voltage roentgen therapy, with no relief. Five years previously she had been told that she had a tuberculous gland, but the mass was not removed because of the presence of an aneurysm. The pain in the left side of the neck became more severe. The mass was not tender or adherent to the skin. Pulsations were seen and felt over the lower pole. The clinical diagnosis was tumor of the carotid body. The growth was excised (August 8), with liga-

TABLE 4.—*Tumors of Miscellaneous Origin*

Case and Sex, Patient Age	Site	Duration	Size	Clinical Diagnosis	Pathologic Diagnosis	Comment
Case 1 J. M. 63	Growth under chin	2 years	"Large, firm, rounded mass" (1st tumor)	1st diagnosis: thyroglossal duct cyst (?) degenerating lipoma	1st, lipo- myxoma; 2d, liposarcoma, recurrent	8 resections made because of recurrence; no further metastases at present
Case 2 F. C. S. 39	Large mass on left side of neck	20 years	44 Gm.; 6 × 4.5 × 3.5 cm.	Submaxillary tumor	Tumor of carotid body	Recovery
Case 3 S. C. 55	Left side of neck	6 to 7 years	52 Gm.; 8 × 5 × 2.5 cm.	Tumor of carotid body	Primary tumor of carotid body	Died; con- firms high mortality with ligation of carotid artery

tion of the carotid artery. The patient died the next day. The tumor consisted of a flat, encapsulated structure weighing 52 Gm. and measuring 8 by 5 by 2.5 cm. The surfaces made by sectioning were variegated, having in places a brownish tint like the adrenal cortex, while the rest was white to pale pink. Microscopically, sections disclosed changes similar to those observed in case 2. The pathologic diagnosis confirmed the clinical conclusions (T. D. R.).

*Comment.*—Liposarcomas are not infrequent tumors which occur in various locations (mediastinum, sole, joints, subcutaneous tissue, omentum). They consist of a mixture of adult fat and embryonic fat cells, fibrous connective tissue and, not infrequently, large granular or smaller round polyhedral cells that "give no hint of their origin" (Ewing). They sometimes exhibit a xanthomatous quality. Once initiated, they run a progressive fatal course if unrecognized and not removed. Like connective tissue structures, they tend to ramify and often fail to betray the extent of their spread. In this respect they are similar to angiomas, which notoriously recur simply because their definition is grossly difficult to detect. The tumor described here was resected eight times before it was eradicated (table 4). Many of these tumors have

been labeled myxomas, fibromyxomas, spindle cell sarcoma or fascial sarcomas, and their true nature has often not been disclosed because the pathologist fails to stain for fat. Several years ago one of us (F. R. M.<sup>13</sup>) had occasion to report on a very large liposarcoma of the omentum. Many others, in all parts of the body, have been recognized, and what was once called a rare type of tumor is now becoming much more common.

Primary tumors of the carotid body are also relatively uncommon. Phelps, Case and Snyder,<sup>14</sup> in a recent report, pointed out that there were then 159 verified cases in the literature. These authors also stated that the tumors are only locally malignant and do not metastasize. There is an apparent increased mortality rate when there is a necessity to ligate the carotid artery, especially in older patients. These tumors do not respond to radiation therapy. Because of their tendency to remain localized, removal should not be undertaken when it is necessary to do extensive ligations in older patients. These factors are borne out by the 2 instances reported here (table 4).

#### GENERAL COMMENT

We have presented a collection of 21 uncommon tumors of the cervical region with their essential clinical and pathologic abnormalities. The specific or nonspecific pattern of these neoplasias is better understood when one analyzes their confused presenting architecture and views them in the light of their embryonic origin.

It is obvious that the intricate modification of the tubal foregut to form the pharynx and all other derivatives is beset with the possibility of isolated embryonic remnants of many varieties, some of which may become neoplastic. It is also probable that different parts of the structures are incomplete in development that later go on to attempted but disordered completion. Such revived embryogenic anlagen, then, later in life appear as aberrant phenomena, namely, a sinus, a cyst, or a vascular or solid, benign or malignant, neoplasm. One must accept the basic notion of Cohnheim's displaced "cell rests," or, what is sometimes more apparent, "arrested embryonic architecture," or admit the reversion of mature cells in order to explain many of these abnormalities.

As has been mentioned by Crile and others, there is an intimate anatomic and apparently functional relation between this foregut epithelium and lymphoid tissue. It is clearly seen in the normal, and is

13. Menne, F. R.: Primary Liposarcoma of the Great Omentum, *Arch. Path.* **22**:823 (Dec.) 1936.

14. Phelps, F. W.; Case, S. W., and Snyder, G. A. C.: Primary Tumors of the Carotid Body: Review of One Hundred and Fifty-Nine Histologically Verified Cases; Report of a Case, *West. J. Surg.* **45**:42 (Jan.) 1937.

accentuated in the abnormal specimen (fig. 20). All such processes as regenerative hyperplasias, papillomas and many of the uncommon tumors show this characteristic epitheliolymphatic intimacy. This design pervades not only the lesions mentioned here but most goiters, cysts of the thyroglossal duct, cysts of the branchial cleft and the more common



Fig. 20.—Photomicrograph showing a papilloma of the buccal mucosa, with subjacent lymph nodes.

malignant neoplasias, notably the so-called lymphoepithelioma described by Ewing. It is not to be implied that when such tumors as the last mentioned or other malignant tumors of the buccal cavity, the nasopharynx, or its accessory derivitions metastasize both epithelial and lymph cells spread as a unit. However, it seems certain that the inherent

defensive nature of embryonic or mature epidermal cells of foregut origin possess the capability of controlling their subjacent complementary lymphoid environment. It is this element that many of the uncommon tumors have in common.

#### SUMMARY

Twenty-two relatively uncommon tumors of the cervical region are reported on, and their clinical and pathologic characteristics are described.

These tumors consist of 4 derived from the parotid gland, 3 of the branchial cleft, 11 from the thyroid gland, 2 from the carotid gland and 1 a liposarcoma of unknown origin.

While uncommon tumors of the parotid gland have a distinctive pattern, they possess clinical characteristics similar to those of the so-called mixed tumors as far as recurrence and benignancy are concerned.

Carcinomas of the branchial cleft originate in ramifying secondarily infected cysts.

The unusual spread or so-called heterotopia of thyroid tissue into adjacent lymph nodes or into more distant organs and tissues is always indicative of neoplasia, regardless of the benign appearance of the metastatic lesion.

Tumors of the parathyroid may be diffuse or circumscribed, clear celled or granular celled, benign or malignant, with characteristic symptoms.

Tumors of the carotid body are localized tumors which attain seriousness because of their investment of the carotid artery, the ligation of which, in removal, is of dire consequence.

Liposarcomas of the neck are of low grade malignancy and may recur because of lack of definition and incomplete removal.

There is a more or less consistent relation between epithelial new growth and lymphoid tissues in many of the embryonic tumors in the cervical region.

Many of these uncommon tumors might well be labeled uncommon tumors derived from developmental errors of the caudal end of the foregut.

Drs. Hunter, Rockey, Pfeiffer, Manlove, Robertson and Larson gave permission for the inclusion of certain cases in this report.

# LIPOBLASTIC MENINGIOMA

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In their admirable and fundamental classification of the meningiomas, Bailey and Bucy<sup>1</sup> included one group, the lipomatous meningiomas, which, largely because of their rarity, has received little attention. Frequently symptomless, they are usually accidentally discovered at autopsy. They do not differ morphologically or histologically from the lipomas found outside the central nervous system. In fact, the only reason for including them with the meningiomas appears to be the fact that they probably are derived from the primitive mesenchyme of the head region, which forms the leptomeninx. That they may have a more direct relation to the common meningiomas is suggested by the tumor to be described, which had a gross and histologic similarity to a meningioma and contained intracellular fat, which seemed to be the product of the normal metabolism of the tumor cells.

## REPORT OF A CASE

An 8 year old girl was first seen by Dr. Douglas N. Buchanan in the Bobs Roberts Memorial Hospital clinic on Feb. 5, 1935, and was admitted to the hospital three days later. Her mother recounted the following history: On the morning of Feb. 23, 1934, while preparing for school, the patient suddenly became unable to talk, although she understood everything said to her. She had no convulsive movements or twitchings of any part of the body. This aphasia lasted about three hours and then completely disappeared. In the fall of 1934 she began to have similar attacks, which lasted only about two minutes and occurred every few weeks. Three weeks before admission the attacks became more frequent, occurring two to four times a day; two weeks prior to admission twitching of the right side of the face and chattering of the teeth were first noticed. During these attacks the eyes rolled upward.

For the first seven months of life she had manifested symptoms of pyloric stenosis, which were controlled with atropine sulfate. At the age of 4½ years she had acute tonsillitis followed by articular pains, for which her tonsils and adenoids were removed. At the age of 6 years she had measles and pertussis, and at 7, chickenpox.

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1. Bailey, P., and Bucy, P. C.: The Origin and Nature of Meningeal Tumors, *Am. J. Cancer* **15**:15-54, 1931.



The maternal grandmother and a maternal great grandmother had died of carcinoma of the uterus and the paternal grandmother of a malignant tumor of the eye. The mother and father were living and well. The patient was the first child. She had a brother thirteen months younger who was living and well but who also had had symptoms of pyloric stenosis in infancy. The third sibling was a boy who had died at 10 months, of congenital heart disease. The fourth child was a girl who had died at 2½ years of age from a sarcoma of the base of the skull. The last pregnancy had been suspected of being ectopic, and after an exploratory laparotomy it had terminated prematurely at seven months. The child had died four hours after birth.

On examination there were no physical or neurologic abnormalities except a soft systolic murmur audible only at the apex of the heart. On lumbar puncture the pressure was 175 mm. of cerebrospinal fluid. The Queckenstedt test elicited normal responses. The fluid removed contained 1 lymphocyte per cubic millimeter and was clear and colorless. The Wassermann reaction was negative. The protein content of the spinal fluid was not increased. Examinations of the blood and of the urine revealed no abnormalities. Roentgenograms of the skull revealed no abnormalities.

The child was discharged from the hospital with instructions to take ½ grain (0.03 Gm.) of phenobarbital three times a day. Her attacks became less frequent and remained confined to the right side of the face. In the early part of June 1935 the attacks began to spread, and for the first time twitchings of the right arm and hand were noticed.

She was admitted to the hospital on June 20 and an encephalogram was taken on June 21. This was considered normal except that there was less air over the left than over the right occipitoparietal region. The ventricles were not distorted or displaced. She was discharged June 23. She continued to have occasional attacks of short duration.

From Feb. 24 to March 13, 1936, she was hospitalized with an attack of acute rheumatic fever. Her recovery was satisfactory.

She was admitted again on May 25 for another encephalogram. Again the only abnormality was the decrease in air over the left occipitoparietal region, which was interpreted as indicating adhesive arachnoiditis. At this admission the reflexes in the right arm were more active than those in the left. After the second encephalographic examination she remained in good health and had no further convulsions.

In the spring of 1939 her family noticed that she was somewhat irritable, did not get along well in school and in general did not seem like herself. Complete neurologic examination in May revealed no abnormality. On August 29 she complained of headaches and blurring of vision for the first time. Examination showed bilateral choking of the optic disk (2 or 3 D.). There was now definite increase in the reflexes of the right side of the body, with absence of the abdominal reflexes on the right. She was admitted to the hospital on September 5.

An electroencephalogram revealed delta waves from the left frontal region. The visual fields were normal except for enlarged blind spots. Lumbar puncture showed an initial pressure of 350 mm. of cerebrospinal fluid. The spinal fluid was otherwise normal. Routine roentgenograms of the skull revealed diastasis of all sutures, with some erosion along the left coronal suture.

On September 8 ventriculography was performed. The ventricular system was markedly displaced to the right, apparently from a space-occupying lesion in the left frontoparietal region. With a preoperative diagnosis of left fronto-

parietal meningioma, an osteoplastic craniotomy was performed. When the bone flap was turned a large, soft, yellowish friable tumor extruded. In the posterior part of the field the dura was intact, but anteriorly it was absent, the tumor completely replacing it. The inner table of the frontal bone was roughened owing to invasion and erosion by tumor. Sharp bleeding during reflection of the bone flap caused a fall in blood pressure necessitating a blood transfusion. Only sufficient tumor was removed to allow replacement of the flap. The patient left the operating room in good condition. After this procedure she showed moderately severe aphasia and right hemiplegia.

After the wound healed she was given seven roentgen treatments of 200 r each between September 19 and September 28. It was hoped by this means to decrease the vascularity of the tumor so that it might be removed later. She was readmitted on October 22, and on October 24 the bone flap was again reflected. Although many vessels in the tumor were thrombosed, smart bleeding was encountered. Transfusion of blood was necessary. A part of the tumor was removed, and again the flap was replaced, much of the tumor being left in situ.

The third and final stage was performed on November 7. At this time the tumor was seen to occupy an extensive area in the temporal and frontal regions, extending from the second temporal convolution to within about 2 cm. of the midline and from a point 4 cm. posterior to the temporal pole forward for about 7 cm. The lateral portion of the sphenoid ridge was exposed by removal of the tumor.

The tumor was attached by a small pedicle in the sylvian region. For fear of a profuse hemorrhage from this region the pedicle was cut, a small nubbin of tumor being left in this region.

Between November 24 and December 12, 3,000 r was given to the operative site in 200 unit doses. Roentgen therapy was resumed Jan. 8, 1940, and a total of 2,200 units was given in 200 unit doses, the last being given January 19.

She was seen May 31. The ocular fundi were normal. The visual fields were full, having gradually enlarged. She still had marked hemiparesis but was able to walk. The right hand was weak and awkward. Stereognosis and position sense were severely impaired in that limb.

She had been attending school and had learned to write with her left hand. Her reading had been hesitant but correct; the anomia was less pronounced. She relearned many things, such as multiplication tables, much faster than a child learning them for the first time.

*Pathologic Picture.*—The specimens before fixation had a bright yellow color which, combined with their fragmented appearance, gave them a peculiar resemblance to an omelet. After fixation this yellow color largely disappeared.

The specimen removed at the first operation weighed 64 Gm. and consisted of a great number of soft, irregularly shaped pieces of friable tissue. On cut section after fixation the surface was egg white and granular. Small oval areas of brownish discoloration indicated perivascular hemorrhage. Rarely was there evidence of softening or necrosis.

The specimen removed from the second operation weighed 26 Gm. and consisted of several pieces of tissue ranging from 5 cm. to less than 1 cm. in diameter. This tissue showed areas of hemorrhagic infiltration on the surface, and in places thrombosed vessels could be seen. On cut section the surface was not uniform as in the first specimen, but gray and yellow trabeculae separated the tumor into white and granular lobules.

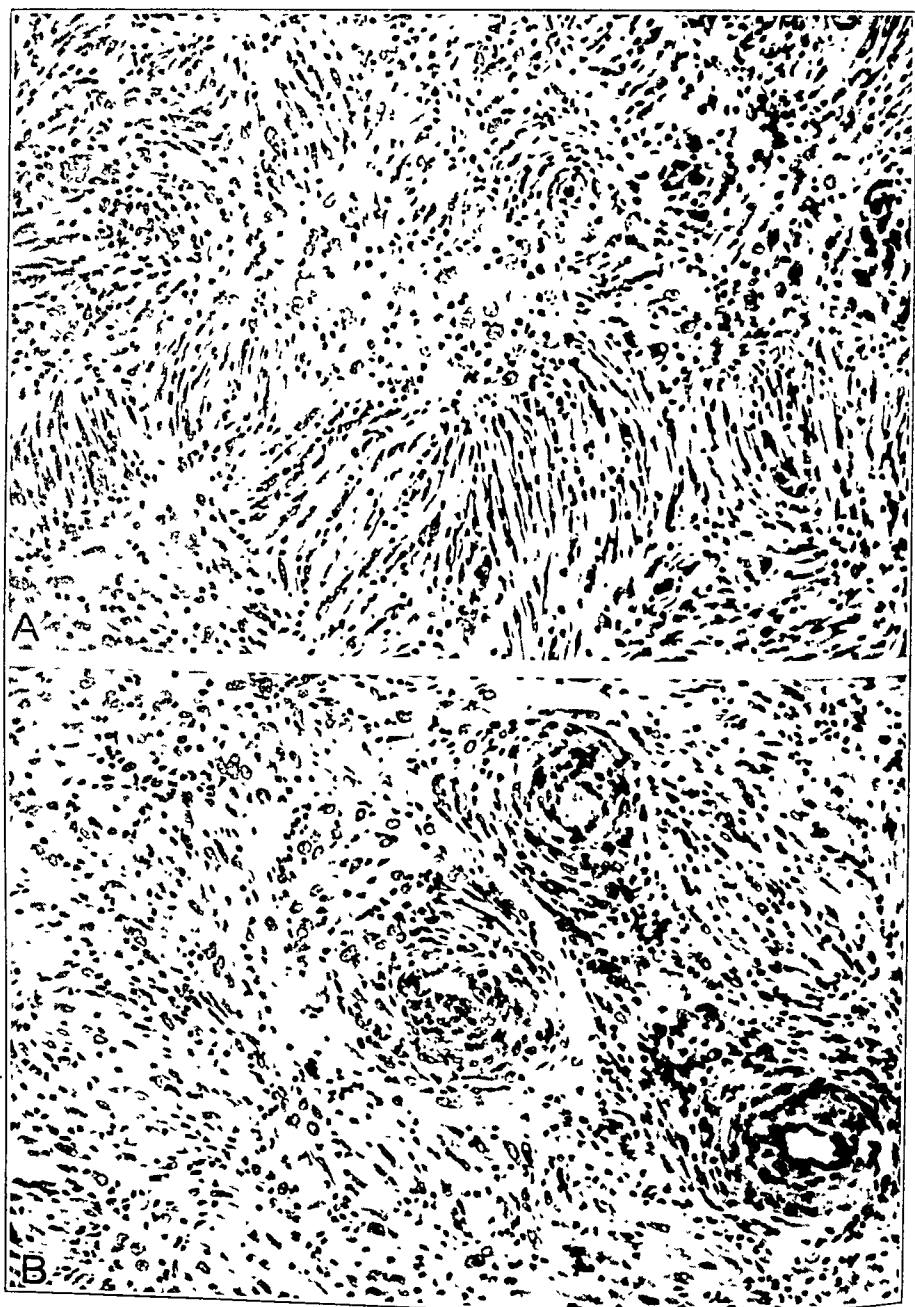


Fig. 1.—*A*, the general structure of the tumor is well shown. *B*, the perivascular whorls give the impression of thickened vessel walls. Hematoxylin and eosin;  $\times 160$ .

The third specimen consisted of three large irregular blocks 7 to 8 cm. in diameter and numerous smaller pieces of tissue. It weighed 126 Gm. The surface of these blocks was grayish and was covered in places with fresh blood. On section, the cut surface of the tumor presented a mottled granular appearance, with yellow and gray streaks penetrating white tissue. There were numerous small brown areas of softening and hemorrhage.

Representative blocks from each specimen were fixed in solution of formaldehyde, Bouin's solution and Zenker's fluid, embedded in paraffin and sectioned.

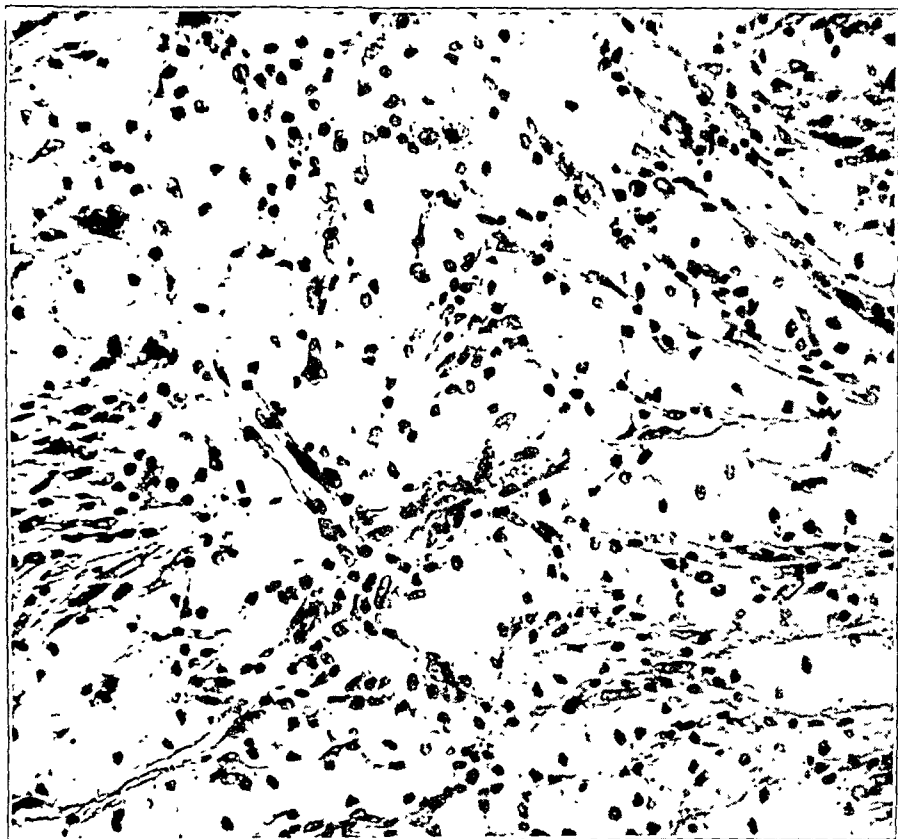


Fig. 2.—All graduation from spindle cells with small vacuoles to large ballooned cells resembling adult fat cells are seen. Such areas were only occasionally observed in the tumor.

The following staining and impregnation methods were used: hematoxylin and eosin, phosphotungstic acid-hematoxylin, Herxheimer's scarlet red stain for fat and Perdrau's method for reticulin.

The tumor was composed of two types of cells, which bore definite relation to each other. The first type, which was numerically much less than the second type, consisted of cells with a faintly granular and eosinophilic cytoplasm arranged in small sheets with very indistinct boundaries. These cells had large oval or round faintly staining nuclei with a few dark chromatin granules and resembled the type of cell observed in meningotheiomatous meningiomas. Smaller, dark-staining oval nuclei, identical with those of the second type of cell, were also present in

the cytoplasmic sheets (fig. 1). This second type of cell was typically an elongated lanceolate cell with distinct boundaries containing a small amount of faintly granular eosinophilic cytoplasm and an oval or bean-shaped vacuole containing fat, which usually lay at one pole of the nucleus. The nucleus was oval or elongated, with a dark-staining thick membrane, and in some instances contained one or several dark staining chromatin granules. In places where these cells were ballooned out by the intracellular fat the nucleus was swollen and eccentrically placed, and its membrane was crenulated. Where the fat accumulation was even more pronounced the cells resembled adult fat cells, the nucleus being flattened out and in one corner (fig. 2).

The cells of the second type had a typical arrangement. They lay parallel, forming rows which radiated to the sheets of the first type of cell or around blood vessels. Thus they formed whorls about blood vessels and, less frequently, about themselves. Because of these perivascular whorls the walls of the blood vessels appeared thickened. The tumor was not very vascular, yet areas of necrosis were rare (fig. 1).

Sections stained for fat showed that the previously mentioned intracellular vacuoles contained fat globules. Within the cell were also smaller droplets of fat, which were not visible in the hematoxylin and eosin preparations. Some fat was present in practically every cell and in the cytoplasm of the cells arranged in sheets. Perdrau preparations showed that the connective tissue was confined to the walls of the blood vessels except for a few areas in which reticulin was present along the elongated cells (fig. 3).

Sections from the frontal bone overlying the tumor showed the presence of lanceolate tumor cells (in the haversian canals and diploic spaces).

The sections from the specimens removed at the second and third operations showed a somewhat different histologic picture. Although the general architecture of the tumor was much the same, the elongated cells which were arranged in parallel or in whorls in the initial specimen were ballooned out in the later blocks. There was more intervascular necrosis and hemorrhage, with a consequent increase in connective tissue. The walls of the smaller blood vessels were thickened.

#### COMMENT

*Pathologic Aspects.*—The histologic appearance of this tumor—the sheets of meningotheiomatous cells and the arrangements of the cells in whorls and palisades—justifies its designation as a meningioma. The presence of intracellular fat does not necessarily indicate that this tumor was a lipoblastic meningioma, for many meningiomas show intracellular and extracellular fat resulting from degenerative changes in the tumor. It may be contended that the large, ballooned-out cells with eccentric nuclei having wrinkled membranes were undergoing degenerative changes. But many of the lanceolate cells with normal-appearing cytoplasm and a nucleus having a smooth membrane and well stained chromatin granules contained globules of fat. That this fat represented a degenerative process in what otherwise appeared to be healthy cells does not seem likely. Especially is this the case when one considers that practically every cell in the tumor contained such fat globules, and yet areas of frank degeneration and necrosis were rare. It seems more

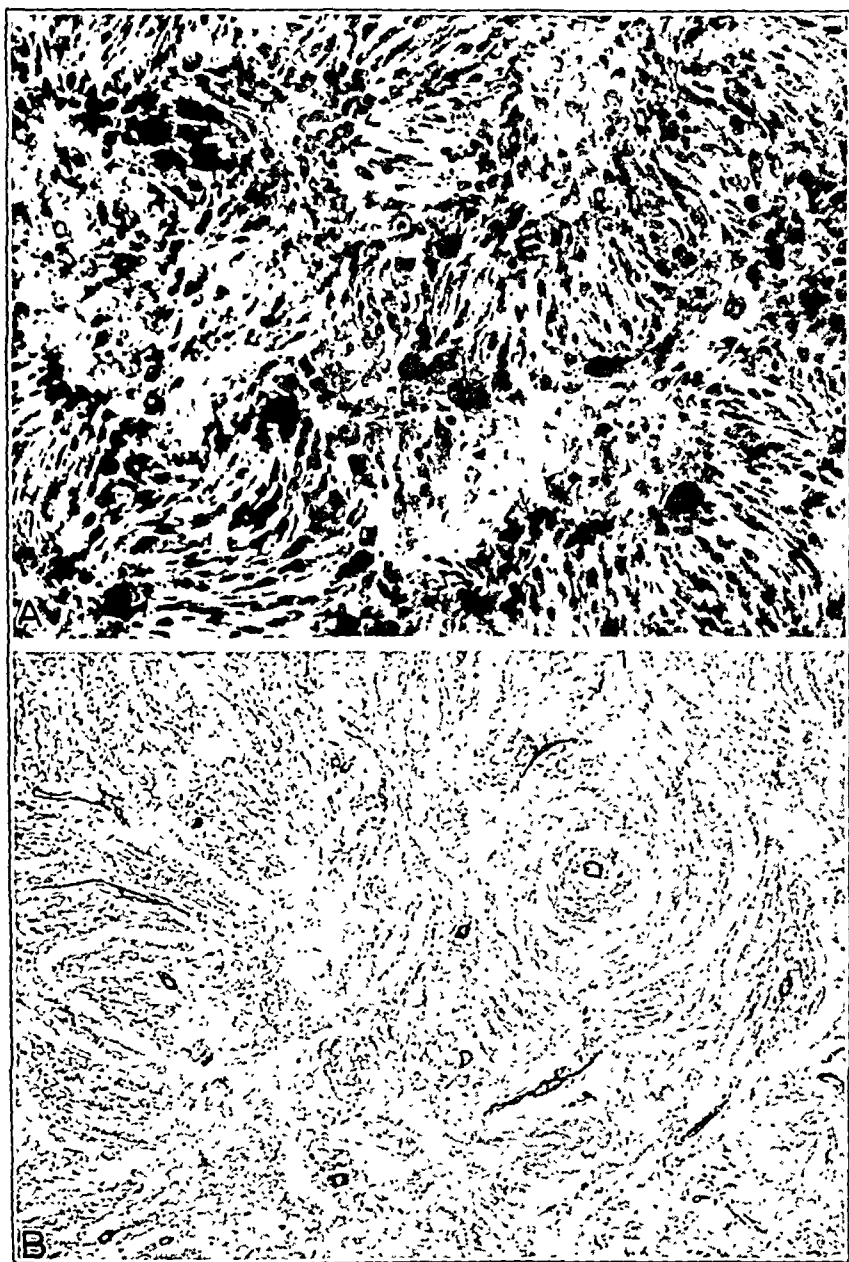


Fig. 3.—*A*, section stained with scarlet red;  $\times 160$ . The fat globules are present in practically every cell. *B*, section stained by Perdrau's method;  $\times 160$ . The reticulin is confined to the vessel walls.

likely that the intracellular fat was the product of the peculiar functional activity of the mesenchymal cells from which the tumor developed. We have been unable to find similar examples in the literature. In their classic review of meningiomas, Cushing and Eisenhardt<sup>2</sup> recognized lipoblastic meningiomas, but their series contained no example. Through the kindness of Dr. Eisenhardt we learned that Penfield and Coburn<sup>3</sup> had presented a case to the American Neuropathological Society in 1939 which resembled this one. They have kindly allowed us to examine slides from their case. Although their tumor did not contain such an abundance of fat as that in the present case and showed slightly more degeneration, it was very similar.

*Clinical Aspects.*—Although supratentorial tumors comprise about one third<sup>4</sup> of the neoplasms of childhood, meningiomas occur infrequently in this age group (1 to 8 per cent of tumors of the brain<sup>5</sup> in patients under 15 years of age). The symptoms of these tumors in childhood are much the same as in adult life. The patient in the case just reported had jacksonian epileptic attacks for about two years. Then, after the administration of phenobarbital, the attacks stopped. It was assumed—and the normal encephalogram seemed to confirm the impression—that the patient was suffering from idiopathic epilepsy. Not until other phenomena developed was the correct diagnosis established. This stresses the necessity of following all patients suffering from convulsive seizures even though sedation relieves the epileptic manifestations.

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2. Cushing, H., and Eisenhardt, L.: *Meningiomas: Their Classification, Regional Behaviour, Life History and Surgical End Results*, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

3. Penfield, W., and Coburn, D.: Personal communication to the authors.

4. Cushing, H.: The Intracranial Tumors of Preadolescence, *Am. J. Dis. Child.* **33**:551-584 (April) 1927.

5. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: *Intracranial Tumors of Infancy and Childhood*, Chicago, University of Chicago Press, 1939.

# FUNGIOUS INFECTIONS OF THE BRAIN

## REPORT OF FOUR CASES

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Although fungous infection of the brain is not a medical curiosity, it is sufficiently unusual to warrant the putting on record of even a small number of cases, such as the 4 reported here.

Several collective studies are on record, one of the most important of which is the review by Boyd and Crutchfield<sup>1</sup> in 1921. In 1928 Jacobson<sup>2</sup> reported 4 cases, in 1 of which there was cerebral involvement, and set the number of recorded cases at that time at 92. In 1936 the California state department of health<sup>3</sup> reported 450 cases, most of which had occurred in California, with 224 deaths. The number of cerebral complications in these cases was not mentioned, but Beck,<sup>4</sup> in a review of 286 cases occurring in California up to 1931, had found intracranial lesions in 18. Courville and Abbott,<sup>5</sup> who in 1938 reviewed the cases in the Los Angeles County Hospital, observed lesions of the nervous system in about 25 per cent of those in which autopsy was performed.

Duckett and Fredeen,<sup>6</sup> in 1936, reported a case of hydrocephalus associated with convulsions in a child 5 years of age. The ependymal linings of the ventricles were affected, but no mention was made of a discrete granuloma. Storts<sup>7</sup> in 1939 reported a case of coccidioidal

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From the Department of Surgery of the School of Medicine of Louisiana State University and from Touro Infirmary.

1. Boyd, M. F., and Crutchfield, E. D.: A Contribution to the Study of Mycetoma in North America, *Am. J. Trop. Med.* **1**:215-289, 1921.

2. Jacobson, H. P.: Coccidioidal Granuloma, *California & West. Med.* **29**: 392-396, 1928.

3. California State Department of Health: Coccidioidal Granuloma in California in 1934-1935, *California & West. Med.* **46**:282, 1937.

4. Beck, M. D., cited by Courville, C. B., and Abbott, K. H.: Coccidioidal Granuloma, Special Bulletin 57, California Department of Public Health, 1931.

5. Courville, C. B., and Abbott, K. H.: Pathology of Coccidioidal Granuloma of the Central Nervous System and Its Envelopes, *Bull. Los Angeles Neurol. Soc.* **3**:27-41, 1938.

6. Duckett, T. G., and Fredeen, R. C.: Coccidioidal Granuloma, *J. Kansas M. Soc.* **37**:111-114, 1936.

7. Storts, B. P.: Coccidioidal Granuloma Simulating Brain Tumor in Child of Four Years, *J. A. M. A.* **112**:1334-1335 (April 8) 1939.



granuloma simulating brain tumor in a child 4 years of age. He stated that this case brought the number of such conditions occurring in children under 5 years of age to 22.

The usual textbooks on medicine, neurology and surgery have little or nothing to say about fungous infections of the brain other than torulosis, which seems to have a special affinity for the nervous system. Grinker<sup>8</sup> mentioned actinomycosis but merely said that it is very rare.

#### REPORT OF CASES

CASE 1.—W. H. S., a white man aged 34, an attorney, was admitted to Touro Infirmary March 21, 1930, and died May 25. His chief complaints were headache and mental confusion.

For the past year he had had headaches, and his business associates, soon after these began, observed that he was having lapses of memory and making frequent mistakes. Recently he had had occasional loss of consciousness while he was working, and periods of mental confusion had become more frequent. For seven months his gait had been unsteady, and for the last few weeks he had needed support while walking.

Five years before admission he had had pneumonia, followed by a pulmonary abscess which healed in a year without surgical intervention. Eight months previously the maxillary sinus had been drained, and three months previously the teeth and tonsils had been removed.

Physical examination showed him to be poorly nourished. He could not walk without assistance, and he was disoriented and had hallucinations. General examination showed nothing of any particular significance. Neurologic examination showed early choking of the disks.

The spinal fluid was clear and under pressure of 26 mm. of mercury; there were 140 cells per cubic millimeter, 90 per cent of which were lymphocytes, and a 3 plus reaction for globulin. The Wassermann reaction was negative. The colloidal gold was markedly reduced in the first zone, and the curve was typically parietic. The chloride content was normal, but the value for dextrose was less than 0.5 per cent. A smear and a culture were sterile. These data were verified on subsequent examinations, and the Wassermann reaction of the blood was repeatedly negative.

Although the patient had been admitted with a tentative diagnosis of abscess of the brain, the absence of any focal signs, together with the spinal fluid picture, led to institution of antisyphilitic treatment, under which he improved rapidly. He began to walk normally, and his mental confusion disappeared. The spinal fluid picture, however, showed no improvement, and the disks did not recede. Within a short time he again became confused. Projectile vomiting developed, accompanied by convulsions, during which the head and eyes were turned to the left. The disks became more edematous, and, although focal signs were still lacking, it was clearly necessary to perform at least a decompression in order to preserve vision.

Operation was performed April 30, forty days after admission, by Dr. L. H. Landry. With the patient under ether anesthesia, a large flap was turned down in the left frontal region, and the dura, which was very tense, was widely opened. Exploration with the needle failed to reveal a tumor, a cyst or an abscess. Because of pressure it was necessary to sacrifice the bone flap in the closure.

8. Grinker, R. R.: *Neurology*, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

The immediate postoperative course was encouraging. The wound healed except in one small area. The patient became rational; there were no further convulsions; vision improved, and he took fluids and food well. Improvement was slow but steady for three weeks, and he was about to be discharged when there suddenly developed high fever, with rapid respiration and cyanosis. Pneumonia was diagnosed by the medical consultant, and there was no response to treatment. Death occurred on May 25, the twenty-sixth postoperative day.

Permission for autopsy was limited to the cranium. The brain showed the usual picture of pressure, with wide, flat convolutions and shallow sulci. The lateral and third ventricles were markedly dilated, as was the upper portion of the aqueduct, which rapidly narrowed, however, to become almost occluded in the midportion. The fourth ventricle was not dilated. The ependyma of this region and the basal meninges showed coccidioidal ependymitis and meningitis.

CASE 2.—L. M. H., a white man aged 24 years, a clerk, was admitted to Touro Infirmary Sept. 23, 1935, was discharged November 23, was readmitted April 18, 1937 and died April 23. His chief complaint was headache.

Six weeks before the first admission the patient had a constant headache, which was occasionally severe but usually dull. He had been very nervous and had lost some weight. For two weeks before admission there had been fever but no chills.

The temperature on admission was 101 F., the pulse rate 85 and the respiratory rate 20. The blood pressure was 120 systolic and 70 diastolic. The patient was emaciated and seemed seriously ill. He moved constantly about the bed, and there were twitchings of the face and tremors of the hands. The sensorium was dulled.

Except for moderate leukocytosis, all examinations of the blood, including agglutinations, showed normal conditions. The spinal fluid immediately after admission was clear and was under a pressure of 8 mm. of mercury. There were 925 cells per cubic millimeter, 95 per cent of which were lymphocytes, and a 3 plus reaction for globulin. The Wassermann reaction and the colloidal gold reaction were negative. The value for chlorides was 645 mg. and that for dextrose 5 to 10 mg. per hundred cubic centimeters. Repeated examinations showed a gradual reduction in the cell count, with lymphocytes always predominant. The concentration of chlorides remained normal, and that of dextrose was reduced. Smears and cultures were consistently sterile.

For two weeks after admission the patient was drowsy and irrational. He wept frequently, and there was urinary incontinence. The temperature was of the septic type, with elevations to 102 F.

Then gradual improvement set in, and he was discharged on November 23, sixty-one days after admission. The diagnosis was influenzal meningoencephalitis. He returned to work and remained well for more than two years.

On March 27, 1937, he had an attack of vertigo, which cleared up within a few days under home remedies. There were no specific complaints, but he did not feel well. On April 10 projectile vomiting developed, followed by restlessness which merged into stupor, and he was brought back to the hospital April 18.

The temperature on admission was 98 F.; the pulse rate was 68, and the respiratory rate was 18. Neurologic examination showed no significant changes in the physical signs. The spinal fluid, though clear, was yellow and was under pressure of 18 mm. of mercury. It contained 200 cells per cubic millimeter and gave a 3 plus reaction for globulin. The course was rapidly downhill, and death occurred April 21, twenty-five days after the first attack of vertigo.

Autopsy showed the arachnoid thick and opaque, with engorged vessels. The brain was flattened, and there was a slight opalescent exudate in the sulci. Adhesions were present between the dura and the base of the brain, and small granulomatous lesions dotted the surface. The ventricles were dilated and the

cerebrospinal fluid cloudy. A large granulomatous mass in the roof of the fourth ventricle blocked the aqueduct. On microscopic examination the pia-arachnoid was seen to be markedly thickened and infiltrated with lymphoid and plasma cells and occasional endothelial cells and neutrophils. The blood vessels were engorged and the underlying tissues edematous. Section showed a papillomatous growth of the lining of the fourth ventricle, and in the wall was an infectious granulomatous reaction not characteristic of any specific cause. Culture of the cerebrospinal fluid revealed a growth of saccharomycetes.

*Comment.*—Obstructive hydrocephalus was present in both these cases, caused in the first by occlusion of the aqueduct and in the second by a granulomatous mass in the roof of the fourth ventricle. Occlusion of the aqueduct is not particularly rare, as Shelden, Parker and Kernohan,<sup>9</sup> Kernohan<sup>10</sup> and Parker and Kernohan<sup>11</sup> have shown, but in none of their cases was the condition due to mycotic infection.

In case 1 the diagnosis on admission was abscess of the brain. This diagnosis was based on the clinical picture and the history of a previous pulmonary abscess. Later the diagnosis was changed to neoplasm, but the operative findings did not support it. As this case is examined in retrospect and in the light of present knowledge, it would seem that the true diagnosis might have been suspected if it had been considered. The patient's home was in Texas, close to the Mexican border, and the spinal fluid picture was consistent with that since reported by Courville and Abbott.<sup>5</sup> Coccidiosis in general strongly resembles tuberculosis, and, as a matter of fact, the first postmortem diagnosis in case 1 was tuberculous meningitis; it was subsequently changed to coccidiosis when the organism was identified. The typical refractile membrane and granular center, as described by these authors and presented in one of their figures, is shown in the accompanying illustration.

It is quite possible that this patient had an abscess of the lung at the time of his death. The pulmonary abscess which had followed pneumonia five years before had never been drained surgically, although it had healed clinically. Five years later cerebral symptoms developed and were temporarily relieved by decompression. Four weeks later, after a satisfactory clinical recovery from operation, he died of a pulmonary complication which clinically was pneumonia. As autopsy was limited to the cranium, the pulmonary observations are not available, but it is significant that a roentgenogram taken shortly before death showed a small area on the right side in which the absence of lung markings suggested destruction of pulmonary tissue. The roentgen picture was

9. Shelden, W. D.; Parker, H. L., and Kernohan, J. W.: Occlusion of the Aqueduct of Sylvius, *Arch. Neurol. & Psychiat.* **23**:1183-1202 (June) 1930.

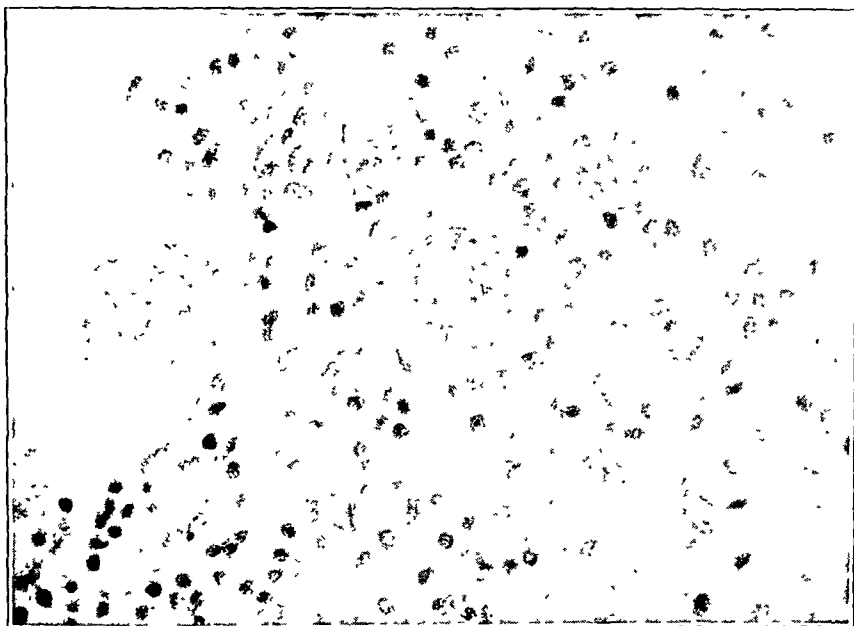
10. Kernohan, J. W.: Cortical Anomalies, Ventricular Heterotopias and Occlusion of the Aqueduct of Sylvius, *Arch. Neurol. & Psychiat.* **23**:460-480 (March) 1930.

11. Parker, H. L., and Kernohan, J. W.: Stenosis of the Aqueduct of Sylvius, *Arch. Neurol. & Psychiat.* **29**:538-560 (March) 1933.

consistent with abscess of the lung, though no actual evidence could be adduced, and there was no clinical evidence of the condition during his hospital stay. It is entirely possible, furthermore, that the roentgen appearance might have been due to the previous abscess.

The diagnosis in the second case was encephalitis of the influenza group. Nothing in the history, physical examination or autopsy disclosed the actual route of invasion of the central nervous system, and the speculations thus introduced are very interesting.

CASE 3.—A white man 35 years of age, a laborer, was admitted to Touro Infirmary Oct. 4, 1938, and died October 14.



*Coccidioides immitis* (case 1). Note the refractile membrane.

This patient had been discharged from the hospital four months before, after an attack of pneumonia from which he had apparently completely recovered. In the interim he had been at work, although for three months he had had frequent headaches, which were not associated with vomiting. On the day of admission, while at work, he suddenly noticed clonic movements of the right arm and of the pectoral and abdominal muscles. The convulsions were checked only by deep anesthesia. When the patient regained consciousness, he stated that a week previously he had been irrational for a short time but had attributed his condition to food poisoning. The headaches had continued as previously during the next few days, with no additional symptoms. For the past twenty-four hours there had been some mental confusion, and paresthesia had been present in the right upper extremity.

Physical examination showed slight weakness on the right side, with greater activity of the tendon reflexes than on the left. The abdominal reflexes were absent on the right. No clonus or abnormal reflexes could be elicited, and the fundi were normal.

Roentgenograms of the head and chest revealed nothing abnormal. The spinal fluid was clear, and the pressure was 8 mm. of mercury. There were 8 cells per cubic millimeter and no globulin. The Wassermann reaction was negative. The colloidal gold curve was slightly elevated in the middle zone.

On October 10, the seventh day after admission, the patient had a second convulsion, resembling the one which had brought him to the hospital. It was followed by hemiplegia and deep stupor. The spinal fluid, although still clear, was under a pressure of 30 mm. of mercury. There were only 4 cells per cubic millimeter, but the globulin reaction was 3 plus. The colloidal gold curve, as previously, was slightly elevated in the middle portion.

Operation was performed April 12 with the patient under ether anesthesia. The diagnosis was abscess of the brain and was confirmed by exploration. The pus showed no growth on culture. Death occurred forty-eight hours later.

Autopsy showed, in addition to the abscess, diffuse bronchopneumonia of the right lung, with encapsulated empyema between the lower lobe and the diaphragm. Cultures of the pus showed pneumococci, *Bacillus influenzae* and *Staphylococcus haemolyticus aureus*. Microscopic sections showed foci of suppuration containing sulfur granules, which led to the diagnosis of actinomycosis.

*Comment.*—This was obviously a fulminating abscess of the brain secondary to pulmonary abscess. Actinomycosis was not suspected until the microscopic sections were studied.

CASE 4.—R. D., a white woman aged 35 years, a housewife, was admitted to Touro Infirmary Aug. 18, 1939, and discharged October 24. The chief complaints were twitching of the muscles of the face, headache, vomiting and paralysis of the right arm.

One month before admission the patient had had a five minute attack of twitching of the right side of the face, during which the mouth was drawn to the right, the eyes deviated and the tongue protruded to the right. A week before admission a similar, more severe attack had occurred, after which the speech was thick and indistinct. Since that time the patient had been unable to name simple objects. Three days later she had noticed weakness in the right arm, which rapidly progressed to paralysis. Vomiting had begun at the same time and had continued.

Four months before admission the patient had stepped on a rusty nail in the back yard of her home in the country. The resulting wound, which was between the first and the second right metacarpal bone, became infected and required drainage. It was still unhealed.

The temperature on admission was 99 F., the pulse rate 72, the respiratory rate 20 and the blood pressure 124 systolic and 80 diastolic. Physical examination revealed paralysis of the right upper extremity. The patient was aphasic, as was illustrated by her inability to name objects, although she could illustrate their use. Otherwise her speech was fairly good. There was slight tenderness to percussion in the left frontoparietal region. There was a weakness, of the central type, of the right side of the face. The fundi were normal. The right foot was swollen and tender but was not reddened or hot. Wounds on the plantar and dorsal surfaces discharged thick pus.

The Wassermann reaction was negative, and the blood picture was within the normal range. Urinalysis revealed no abnormality. The spinal fluid was clear and under a pressure of 440 mm. of water; there were 6 cells per cubic millimeter and a trace of globulin. The Wassermann reaction was negative, and there was a slight elevation of the colloidal gold curve in the first zone. The value for chlorides

was 690 mg. and that for the dextrose 93 mg. per hundred cubic centimeter. A smear and a culture were sterile.

Roentgen examination of the head showed the pineal body calcified; it was shifted to the right, downward and backward. Roentgenograms of the chest revealed no abnormalities, and roentgenograms of the right foot showed osteoporosis.

Operation was performed April 25 with the patient under ether anesthesia, after a diagnosis of tumor of the brain. Exploration revealed an abscess of the left midfrontal region, for which drainage was instituted. Studies of the pus showed colonies of mycelial branching filaments containing sporelike bodies and a form of mycelium-producing organism. Fresh preparations of pus from the foot showed mycelial organisms of the same morphologic structure as those obtained from the brain. After careful study the opinion was arrived at that this growth was mycetoma, or Madura foot.

The patient improved slowly after operation. The abscess cavity was extruded and removed with the electrosurgical loop. The general condition was good on discharge, but there was little improvement in the hemiplegia, and the speech, although improved, was still markedly deficient. The patient exhibited considerable emotional instability, frequently laughing or crying without reason.

Epithelium was slowly covering healthy granulations in the wound in the head. The foot had twice been widely opened and drained but was not improved, and it seemed clear that amputation would ultimately be necessary. During the entire illness there was no sign of abscess of the lung either clinically or by roentgen examination.

The patient returned to her home in the country after her discharge and for a time seemed fairly well. About four months after leaving the hospital she died very suddenly, and autopsy was not permitted.

*Comment.*—Although a number of cases of mycetoma have been reported in North America, some as far north as Massachusetts and Canada, most have occurred in Mexico or near the border. This patient's foot did not present the typical picture of Madura foot, which usually develops very slowly and extends over a period of years. It is quite possible, however, that the condition might have run the usual course had she lived long enough.

#### SUMMARY

Four cases of fungous infection of the brain are reported, in each of which the condition was due to a different cause (case 1, coccidiosis; case 2, saccharomycosis; case 3, actinomycosis; case 4, infection with a mycelium-producing organism).

In 2 cases the lesions were abscesses of the brain, and in 2, encephalomeningitis.

In all 4 cases the diagnosis was verified by microscopic examination, and in 3 it was confirmed by autopsy. In the fourth case the culture yielded bacteria.

The preoperative diagnosis in 2 cases was tumor of the brain.

All 4 cases terminated in death.

Dr. John A. Lanford, director of laboratories at Touro Infirmary, made the pathologic studies in all of these cases.

# MALIGNANT RENAL NEOPLASMS IN CHILDREN

## REVIEW OF TWENTY-SIX CASES

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AND

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The Wilms tumor is the most common malignant growth affecting the kidneys of infants and children. It is estimated that tumors of the kidney comprise approximately 25 per cent of all malignant tumors occurring in childhood.

In 1828, Gairdner<sup>1</sup> reported the first case of sarcoma of the kidney in an infant. Eberth<sup>2</sup> in 1872 first described this type of tumor and suggested that it is derived from remnants of the wolffian body. In 1875 Cohnheim<sup>3</sup> and in 1886 Ribbert<sup>4</sup> stated that the tumor has its beginning in aberrant germ plasma from the primitive segments. Weigert<sup>5</sup> in 1876 stated the belief that the tumor is a congenital adenocarcinoma of the kidney, probably derived from misplaced cell rests. Osler<sup>6</sup> in 1879 described 2 cases of striated myosarcoma of the kidney, but he offered no theory as to the origin of the growths. Brosin<sup>7</sup> in 1884 also stated that the tumor is of congenital origin, and he mentioned 1 case of congenital sarcoma of the kidney. Likewise, Brock<sup>8</sup> in 1895 averred that the derivation is from embryonic cell inclusions embedded in the urogenital fold.

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1. Gairdner, E.: Case of Fungus Haemetodes in the Kidneys, Edinburgh M. & S. J. **29**:312-315, 1828.

2. Eberth, C. J.: Myoma sarcomatodes renum, Virchows Arch. f. path. Anat. **55**:518-520, 1872.

3. Cohnheim, J.: Congenitales, quergestreiftes Muskelsarkom der Nieren, Virchows Arch. f. path. Anat. **65**:64-69, 1875.

4. Ribbert: Ueber ein Myosarcoma striocellulare des Nierenbeckens und des Ureters, Virchows Arch. f. path. Anat. **106**:282-295, 1886.

5. Weigert: Adenocarcinoma renum congenitum, Virchows Arch. f. path. Anat. **67**:492-499, 1876.

6. Osler, W.: Two Cases of Striated Myosarcoma of the Kidney, J. Anat. & Physiol. **14**:229-233, 1879.

7. Brosin: Congenitales Nierensarcom mit quergestreiften Muskel-fasern, Virchows Arch. f. path. Anat. **96**:453-461, 1884.

8. Brock, G.: Eine Geschwulst der Nierengegend mit quergestreiften Muskel-fasern, Virchows Arch. f. path. Anat. **140**:493-502, 1895.

It is obvious that considerable confusion existed as to the exact origin or derivation of this neoplasm. This led Wilms<sup>9</sup> in 1899 to record his monograph on the origin and derivation of this tumor. His theory still is the most widely accepted one. He emphasized that several tissues observed microscopically in these tumors cannot be derived from the wolffian body. Rather, their origin is from the primitive, undifferentiated mesodermal tissue which can give rise to myotome (skeletal muscle), sclerotome (vertebrae), nephrotome (wolffian body) and mesenchymal tissue, which gives rise to smooth muscle in the course of normal development.

Several theories have been advanced in recent years, but these are reiterations of the previously mentioned ones. However, Ewing<sup>10</sup> in 1934 stated that the tumors originate from the renal blastema, and he stressed the role played by metaplasia.

Recently one of us (C. C. H.) operated on a girl 4 years of age who had a Wilms tumor which was of such interest<sup>11</sup> that it prompted a review of our cases to add our statistics to those already presented in the literature.

#### MACROSCOPIC PATHOLOGIC PICTURE

The tumor may involve any part of the renal parenchyma. It is grayish white, solid and firm and, in general, cannot be freed from the remainder of the kidney. It is well demarcated from the renal parenchyma, and nodules frequently are present in the substance of the tumor and in the remainder of the kidney. As growth takes place, softening and hemorrhage in various parts of the tumor are noted. When the gross specimen is sectioned, scattered cysts may be encountered. The capsule of the tumor is tense and bulges on the external surface, giving the appearance of an irregular mass. Since the tumor is encapsulated, early invasion of the renal pelvis does not occur. When the tumor increases in size the adjacent renal parenchyma undergoes pressure atrophy, while, on the other hand, areas of normal renal parenchyma are present. Areas of necrotic degeneration may be present in the neoplasm. The pelvis of the kidney may appear normal or may be compressed by the growth.

#### MICROSCOPIC PATHOLOGIC PICTURE

Microscopically, the tumor presents many types of tissue in one mass. All stages from undifferentiated to well defined differentiated cells derived from the three germinal layers may be seen; that is, smooth

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9. Wilms, M.: *Die Mischgeschwülste der Niere*, Leipzig, Arthur Georgi, 1899, pp. 1-90.

10. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

11. Higgins, C. C., and Shively, F. L., Jr.: Wilms' Tumor (Adenomyosarcoma) of Kidney in Children: Report of Case, *Cleveland Clin. Quart.* 6:265-274 (Oct.) 1939.



muscle, striated muscle, cartilage, fat and bone. Areas of glandular tissue are observed in which some of the acini are well defined, while in other areas such well demarcated acini are not discernible. The tumor has a fibrous tissue stroma. It is uncommon to find only one type of tissue predominating, and a multiplicity of tissues is usually seen in a given section. Likewise, the renal vein or its branches may be involved by the tumor. According to Ladd,<sup>12</sup> the tumor is characterized by (1) a variegated histologic structure; (2) rapid growth after a period of slower activity; (3) the common occurrence of hemorrhage and necrosis, which may lead to rupture of the capsule; (4) the possibility of invasion of the renal vein or the pelvis of the kidney; (5) the tendency to attain a large size before metastasis occurs and (6) the frequency of local recurrence and metastasis to regional lymph nodes or remote metastasis through the blood stream to the lungs.

#### AGE AND SEX

In Ladd's<sup>12</sup> series the average age of the patients was 2 years and 3 months. The youngest patient was 2 months of age, and the oldest was 7 years of age. There were 26 girls and 19 boys. In other series there has been a slight predominance of boys; in Kretschmer's<sup>13</sup> group 18 patients were boys and 6 were girls.

In this series there were 11 boys and 15 girls, the average age on admission being 3½ years. The youngest patient was 3½ months of age, and the oldest was 19 years of age.

#### SIDE INVOLVED

The tumor involved the right kidney in 16 cases and the left kidney in 10. Bilateral involvement was not present in any of this group. In Ladd's<sup>12</sup> series, the occurrence of the tumor was divided equally between the two kidneys.

#### CLINICAL ASPECTS

Progressive enlargement of the abdomen is the first apparent abnormality (fig. 1). This was noted in 59.8 per cent of this series and was present at the time of examination in 25 of the 26 children. The mother frequently observes the unusually large abdomen, which progressively becomes more prominent. In some instances the mass itself is felt by the mother or the nurse while bathing the child. Enlargement of the abdominal mass often is unaccompanied by pain, and if pain is experienced it usually is dull and aching. Pain was the initial symptom in

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12. Ladd, W. E.: Embryoma of Kidney (Wilms' Tumor), *Ann. Surg.* **108**: 885-902 (Nov.) 1938.

13. Kretschmer, H. L.: Malignant Tumors of Kidney in Children, *J. Urol.* **39**:250-275 (March) 1938.

38 per cent and occurred as the disease progressed in 62 per cent of this series.

Hematuria was the initial symptom in 12.2 per cent and occurred during the course of the disease in 19.2 per cent of the children.

It is of interest that an elevation of temperature of obscure origin may be observed. In this series, an elevation of temperature at the initial examination was present in 42 per cent, and occurred later in the



Fig. 1.—*A*, large Wilms tumor of the right kidney. *B*, Wilms tumor of the left kidney.

disease in 60 per cent, of the children. After removal of the kidney the temperature returned to normal.

Various other symptoms, such as nausea, vomiting, shortness of breath and constipation, may occur, due to pressure of the mass on adjacent structures. Loss of strength, loss of weight and anemia are evident as the disease progresses. It is thus evident that in many instances symptoms referable to the urinary tract do not predominate in the clinical picture, and a mass in the abdomen is the first abnormality discernible.

## DIAGNOSIS

With the present facilities for investigation of the kidneys, establishment of an accurate diagnosis is not difficult. The clinical history and an abdominal tumor which is gradually increasing in size in an infant or a child immediately suggest the possibility of a Wilms tumor. The mass usually is solid, firm and not tender or fluctuant. Occasionally the tumor is nodular, but more often it is smooth and rounded. Some mobility may be present in the smaller tumors, but the large masses are usually not mobile.

The initial roentgenogram reveals a large shadow in the soft parts, which may extend across the midline of the abdomen. The intestines may be displaced to the opposite side of the abdomen, and the stomach is elevated upward. Calcifications may be demonstrable. Excretory urographic study is a valuable aid in establishing the diagnosis. Occasionally, however, visualization of the renal pelvis or calices is not satisfactory, owing to the large size of the mass. Certain contraindications to intravenous injection of contrast mediums may be present, and it is well to recall that subcutaneous injection is satisfactory. Twenty cubic centimeters of 35 per cent diodrast is diluted with 80 cc. of physiologic solution of sodium chloride, and 50 cc. of the solution is injected subcutaneously over each scapula. Films are made at intervals of ten, twenty and thirty minutes after the injection. Intravenous urograms may reveal distortion of the renal pelvis, or the pelvis may not be visualized (fig. 2). For more accurate interpretation, retrograde pyelograms are more satisfactory, visualization being much clearer than that secured by intravenous or subcutaneous injections of diodrast. Flattening of the pelvis and compression of the calices may be revealed. Ladd<sup>12</sup> has stated that a normal-appearing pyelogram may be obtained in the presence of a large tumor. In this series, however, various deviations from the normal pyelogram were noted in every instance.

Various other tumors must be considered in establishing an accurate diagnosis. Sympathetic neuroblastomas arising from the adrenal gland and of sufficient size to be palpated by abdominal examination reveal downward displacement of the kidney when the pyelogram is studied. Aside from this the pyelogram may be normal. Metastases, as a general rule, also occur before the growth attains the usual size of a Wilms tumor. Polycystic kidney likewise may be differentiated by pyelographic studies and tests of renal function. In a like manner, large hydronephroses produced by aberrant vessels or congenital strictures or bands may be ruled out by retrograde or intravenous pyelograms. Although solitary cysts of the kidney in children rarely attain a sufficient size to offer a diagnostic problem, we have observed 1 child in whose case a diagnosis of Wilms tumor had been made and a hopeless prognosis offered. Exploratory operation revealed an enormous solitary cyst at

the lower pole of the kidney. Retroperitoneal tumors and cysts also must be ruled out, as such tumors may attain a considerable size before being noted. Displacement or rotation of the kidney may be present with or without filling defects in the renal pelvis, and displacement of the ureter may also occur. Stereoscopic films should be secured to demonstrate the relation of the tumor to the kidney. Enlargement of the spleen or ovarian tumor is less difficult to differentiate from the Wilms tumor by abdominal palpation, rectal examination and pyelographic studies.

Aspiration biopsy as an aid to diagnosis has not been used in any case in this group.



Fig. 2.—*A*, Wilms tumor of the right kidney. *B*, intravenous urogram showing a Wilms tumor of the left kidney.

Thus, by correct interpretation of the clinical history, by abdominal palpation and by excretory urographic or retrograde pyelographic study a correct diagnosis may be established in the majority of cases.

#### TREATMENT

After the diagnosis has been established, the treatment must be considered. Kerr,<sup>14</sup> Priestley and Broders,<sup>15</sup> Kretschmer,<sup>13</sup> Adams and

14. Kerr, H. D.: Treatment of Malignant Tumors of Kidney in Children, *J. A. M. A.* **112**:408-411 (Feb. 4) 1939.

15. Priestley, J. T., and Broders, A. C.: Wilms' Tumor: Clinical and Pathologic Study, *J. Urol.* **33**:544-551 (June) 1935.

Hunt<sup>16</sup> and others have recommended preoperative irradiation followed by nephrectomy and postoperative roentgen therapy.

As a general rule, a Wilms tumor is radiosensitive and diminishes remarkably in size during the course of roentgen therapy. However, Kretschmer<sup>13</sup> reported 1 case in which reduction did not follow roentgen therapy. Dean<sup>17</sup> cited the case of a small girl who seemingly is free from disease three years and a few months since the instigation of roentgen therapy. He stated that there is no evidence of function in the treated kidney and that the mass previously present cannot be palpated at present. An area of calcification 4 by 6 cm. is demonstrable in this region.

*Data in Twenty-Six Cases of Wilms Tumor*

Treatment	No. of Cases	Duration of Follow-Up														
		0 to 4 Months			5 to 8 Months			9 to 12 Months			13 to 24 Months			25 to 60 Months		
		A	D	L*	A	D	L	A	D	L	A	D	L	A	D	L
Operation alone.....	8	5	2	1	5	2	1	4	3	1	2	5	1	2	5	1
Operation and preoperative roentgen therapy.....	4	4	0	0	1	1	2	1	1	2	1	1	2	1	1	2
Operation and postoperative roentgen therapy.....	6	2	2	2	1	3	2	0	4	2	0	4	2	0	4	2
Operation and preoperative and postoperative roentgen therapy.....	3	2	0	1	2	0	1	2	0	1	1	1	1	1	1	1
No operation or roentgen therapy.....	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0	2
Roentgen therapy advised and refused.....	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0	2
Palliative roentgen therapy	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Totals.....	26	13	4	9	9	6	11	7	8	11	4	11	11	4	11	11
Number living.....	4															
Number dead.....	11															
Number lost trace of.....	11															

\* A, alive; D, dead; L, lost trace of.

Ladd<sup>12</sup> stated: "It is possible that preoperative irradiation facilitates the operation and reduces the immediate operative mortality only at the sacrifice of an increased late mortality." It is generally conceded, however, that the preoperative irradiation is accompanied by reduction in the size of the tumor; the immediate operative mortality is lowered, and the tumor, being reduced, can be removed without manipulation, which may cause dissemination of the tumor cells.

In this series, nephrectomy was performed in 20 cases, or 77 per cent of the 26. Four patients were deemed inoperable because of extensive distant metastasis or unusually pronounced involvement in the affected area. Of the remaining 2, with extensive and seemingly hopeless disease, roentgen therapy was advised for 1, but this was refused by the parents.

16. Adams, P. S., and Hunt, H. B.: Differential Diagnosis of Wilms' Tumor Assisted by Intramuscular Urography, *J. Urol.* **42**:689-708 (Nov.) 1939.

17. Dean, A.: Personal communication to the author.

The second child was brought to the clinic in a moribund condition, and the parents refused to place the child in the hospital. A summary of the results of operation, with or without roentgen therapy, is given in the accompanying table.

#### SURGICAL TECHNIC

In the majority of instances adequate exposure may be secured through the usual posterolumbar incision, especially after reduction of the tumor by roentgen therapy. The vascular pedicle is isolated, clamped and divided before the kidney is manipulated, in order to prevent dissemination of the tumor cells. Similar precautions should be used in removal of a hypernephroma of the kidney in an adult. After the pedicle has been divided, the kidney is mobilized and removed, with as much of the perirenal fatty tissue as possible. If preoperative irradiation has not been employed and a large mass is present, the transperitoneal approach offers immediate isolation and division of the renal pedicle before the kidney is mobilized. A rectus or pararectus incision is adequate and is carried down through the peritoneum. The ascending or descending colon is reflected to the opposite side; the pedicle is isolated and divided. Again, as much as possible of the perirenal fatty tissue should be removed with the kidney. The immediate operative mortality in this series was 3 per cent.

#### RESULTS

In our series, nephrectomy alone was the treatment in 8 cases, operation with preoperative roentgen therapy in 4 cases, operation and postoperative roentgen therapy in 6 cases and operation with preoperative and postoperative roentgen therapy in 3 cases. Two patients were brought to the clinic in a moribund state, and no therapy was advised. Roentgen therapy was advised in 2 cases but was refused by the parents. In the remaining case palliative roentgen therapy was given.

There were 13 patients living, 4 dead and 9 lost trace of at the end of four months; 9 living, 6 dead and 11 lost trace of at the end of eight months, and 7 living, 8 dead and 11 lost trace of at the end of twelve months. At the end of five years, 4 were living and well (1 for forty-one years, one for thirteen years, one for six years and one for six months); 11 were dead, and 11 were lost trace of in our follow-up investigation (see accompanying table).

#### PROGNOSIS

The prognosis for this group of patients is grave. From a review of the literature it is rather difficult to draw conclusions as to the advantage of one type of treatment over another. This is due to incomplete fol-

low-up. Confirmatory microscopic study is often lacking. In a recent series of 7 cases cited by Kretschmer,<sup>13</sup> 1 child received preoperative irradiation followed by nephrectomy and postoperative radiation and is living three years and four months after operation. A second patient is living two years and six months after operation; of the remaining patients, 5 died within one year and six months, one year, six months, six months and one month after operation respectively. He also mentioned 1 patient, reported on in a previous series, who is living and well nine years after operation. This patient did not receive preoperative irradiation.

Of 20 patients cited by Priestley and Broders<sup>15</sup> on whom nephrectomy was performed, 15 are dead, 4 are living and 1 was not traced. Campbell<sup>18</sup> cited a three year cure of a patient who did not receive preoperative irradiation and a fifteen month cure of a patient who had received irradiation. Mintz,<sup>19</sup> in reviewing the records of 7 patients with Wilms tumor who were operated on at the Massachusetts General Hospital, stated that all of these patients died within six months after nephrectomy. Of a series of 45 patients in the surgical service of the Children's Hospital in Boston reviewed by Ladd,<sup>12</sup> 31 have died. Of this group of 31, all but 1 had a recurrence or died within one year of operation. In a series of 28 patients operated on in the last ten years, 2 died from the operation, and 12 died later of the malignant disease. Ladd stated that of 14 patients still living, 11 may be classified as probably cured, the length of time since nephrectomy varying from one and one-half to nineteen and one-half years.

With new roentgen therapy apparatus and changes in administration of therapy in recent years, better results may be anticipated. At present, however, it is our impression that preoperative irradiation followed by nephrectomy and postoperative therapy offers the most to the patient and is the procedure generally accepted at present.

#### SUMMARY

Twenty-six cases of the Wilms tumor are presented. In 20 nephrectomy was performed. There were no cases in which irradiation was used alone, and in only 1 case were palliative measures instituted.

18. Campbell, M. F.: Primary Malignant Tumors of Urogenital Tract in Infants and Children, *J. A. M. A.* **109**:1606-1611 (Nov. 13) 1937.

19. Mintz, E. R.: Embryoma of Kidney in Infant with Osseous Metastases: Report of a Case, *J. Urol.* **31**:79-86 (Jan.) 1934.

# ABSOLUTE MUSCLE POWER

## THE INTERNAL KINESIOLOGY OF MUSCLE

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If the physiology of muscular contraction is reviewed in the light of internal muscle mechanics, a new approach to the physiology of tendon surgery is opened. Certain internal rearrangements must occur in the structure of the muscle after its range has been lengthened, shortened or changed. In the study of these rearrangements the length-tension curve is of primary importance.

### 1. FUNCTION OF THE INTERNAL STRUCTURE OF MUSCLE IN THE TRANSMISSION OF FORCE

The muscle fiber is an elastic tissue with physical properties varying greatly between the relaxed and the stimulated, or contracting, state. A length-tension curve may be constructed to express the behavior of the physical property to be emphasized here, namely, elasticity. If a resting muscle were stretched out and its length-tension relations plotted, a curve would be obtained resembling that shown by the dotted line in figure 4. A maximally stimulated parallel-fibered muscle would follow the path shown in the same figure by the solid line. This line is straight, showing that stimulated muscle is perfectly elastic, while resting muscle is not.

Fick<sup>1</sup> and von Recklinghausen have determined the value of the maximum developed tension at one point in the curve—the “resting length.” Since this is the length of the muscle when just stretched out by a minimal weight, it is the length at which passive resistance to stretch just begins to become apparent and, as will be shown later, is near the maximum physiologic length of the muscle. They found this tension proportional to the cross-sectional area of the muscle (Fick, 6 to 10 Kg. per square centimeter; von Recklinghausen, 3.6 Kg. per square centimeter).

This value has been used to determine the maximum realizable work in life by multiplying this force by the range of the excursion of the tendon insertion ( $\text{Force} \times \text{distance} = \text{work}$ ). But the force varies

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Condensation of a thesis submitted to the faculty of the Graduate College of the State University of Iowa in partial fulfillment of the requirements for the degree of *Master of Science in Orthopedic Surgery*.

1. Fick, cited by Steindler,<sup>5</sup> p. 76.



throughout the distance—varies with the length of the muscle. In reality, the work will be equal to the distance multiplied by the average force. If the length-tension “curve” is a straight line (as it is in parallel-fibered muscles), then the average force will be equal to the force at midrange. Hence, work would equal the range multiplied by the tension at the midpoint of the range.

This is true only of parallel-fibered muscles and, consequently, of individual muscle fibers. The length-tension curves of a parallel-fibered muscle and of its component muscle fibers are necessarily of the same shape. If the curve of the muscle is a straight line, the curve of its fiber will be a straight line. This is not true of those pennated muscles in which the fibers are not parallel to the tendon.

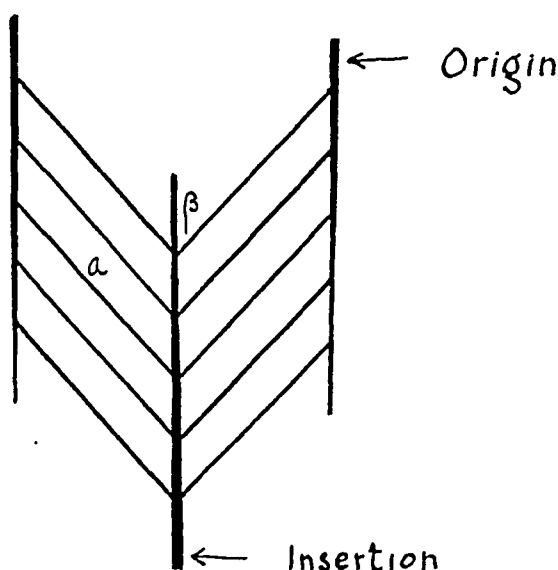


Fig. 1.—Diagram showing the manner in which the muscle fibers run from the origin to the insertion of the muscle. See text for explanation.

The muscle fibers (*a*) in figure 1 may be considered as running directly from the origin to the insertion of the muscle. In other words, the central tendon, being practically inextensible, may be considered as a prolongation of the insertion up into the center of the muscle. The central tendon makes possible a muscle with a short, powerful range, whose long axis is in the long axis of the limb instead of transverse.

It is obvious that the greatest tension (and the least range) for a given weight of muscle will be obtained when there is no more than one cell length between the origin and the insertion as represented by the central tendon. This is the ultimate of modification toward high power and low range. The longer the muscle fibers are, the more range is increased at the expense of power. The central tendon, therefore, is a machine which yields a mechanical advantage to a muscle, just as a

system of pulleys may give a man a mechanical advantage, enabling him to lift a greater weight, but only by diminishing the distance it traverses. In either case (under optimum conditions), the work put into the machine is equal to the work done by the machine. Each muscle has its own "gear ratio"—the parallel-fibered ones cover a great distance with little power; the pennated ones are geared to cover variously smaller distances with correspondingly increased power.

In addition to this, each non-parallel-fibered muscle's gear ratio is constantly varying within the stroke cycle or contraction, the effective component of force (cosine beta, fig. 1) being greatest when the fiber is most nearly parallel to the tendon (extended), and least when it is most nearly perpendicular (contracted).

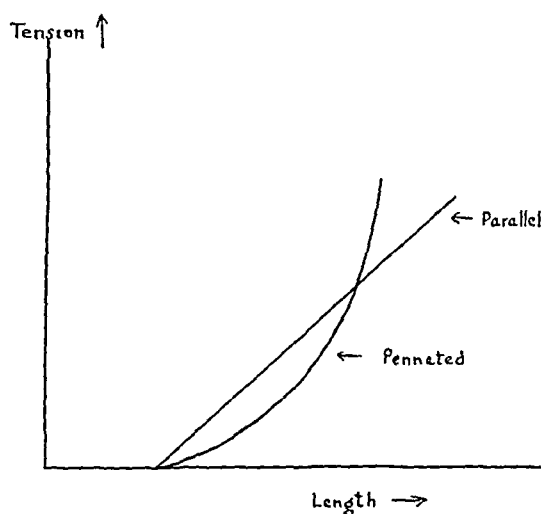


Fig. 2.—Total length-tension line of a parallel-fibered muscle.

This variation in gear ratio is in addition to the variation in developed tension with variation in initial length and tends to accentuate it, changing the length-tension curve from a straight line to a curve.

## 2. RELATION OF THE PHYSIOLOGIC RANGE TO THE LENGTH-TENSION CURVE

Figure 2 shows the total length-tension line of a parallel-fibered muscle. What part of this line is utilized in the physiologic range of joint motion? Is this a constant part of the whole in various muscles?

Certainly it cannot be the whole range, for a muscle still has considerable contractile power left at the point of maximum shortening in life. The quadriceps muscle, for instance, can hold the leg fully extended against considerable force. It seems likely that nature would select the most efficient part of the total range for the physiologic range—a part which would put full extension in life somewhere near the end of the

total range, where large tensions are developed (though not so far that passive resistance to stretch would inhibit full joint range) and yet leave an appreciable tension at full flexion.

The Weber-Fick law<sup>2</sup> states that muscle fibers are shortened to one-half their extended length in full physiologic contraction. This means that, no matter what the physiologic range of the tendon may be, the muscle fibers are so arranged that this range represents a 50 per cent shortening of all fibers. Measurements made on a human cadaver tend to substantiate this.

For example:

Muscle	Fiber Length at Full Extension, Cm.	Contraction Range, Cm.
Brachioradialis .....	18	10.7
Extensor carpi radialis longior.....	12	6.8
Flexor hallucis longus.....	5.7	2.8
Extensor indices proprius.....	8	4
Triceps (medial and lateral heads).....	10.5	5.8
Brachialis .....	14	8
Peroneus brevis .....	3.5	1.6

Consequently, the physiologic range will have to be marked off on the length-tension curve in such a way that the maximally contracted length in life will have to be about one-half the maximally extended length. A glance at the curves in figures 2, 3 and 4 will show that this range may be placed at any one of innumerable positions along the line and still satisfy these prerequisites. What part of this line constitutes the normal range in life, and is it the same in all muscles?

It may safely be assumed that the maximum work done during the total contraction range is proportional to the weight of muscle tissue, since it represents the sum of the work of the constituent sarcomeres.<sup>3</sup>

Now if the physiologic range represents a constant proportion of the total range, the maximum work done in a physiologic contraction must also be proportional to the weight of muscle tissue. Conversely, if the work done is found to be constantly proportional to the muscle weight, then the physiologic range must make up a constant proportion of the total range. This relation is very important and will be referred to again later.

2. Fick, R.: Ueber die Länge der Muskelbündeln, *Ztschr. f. orthop. Chir.* 38:1, 1918.

3. This is corroborated by the work of A. V. Hill (*Muscular Movement in Man*, New York, McGraw-Hill Book Company, 1927, p. 81; cited by Sterling, E. H.: *Principles of Human Physiology*, ed. 7, Philadelphia, Lea & Febiger, 1936, p. 145), who found the work done (area of length-tension curve) constantly proportional to  $\frac{TL}{4}$ . But  $T$  = tension developed at resting length—a function of cross-sectional area, and  $L$  = resting length. Therefore,  $TL$  = volume (or weight). Hence the work done is proportional to the weight.

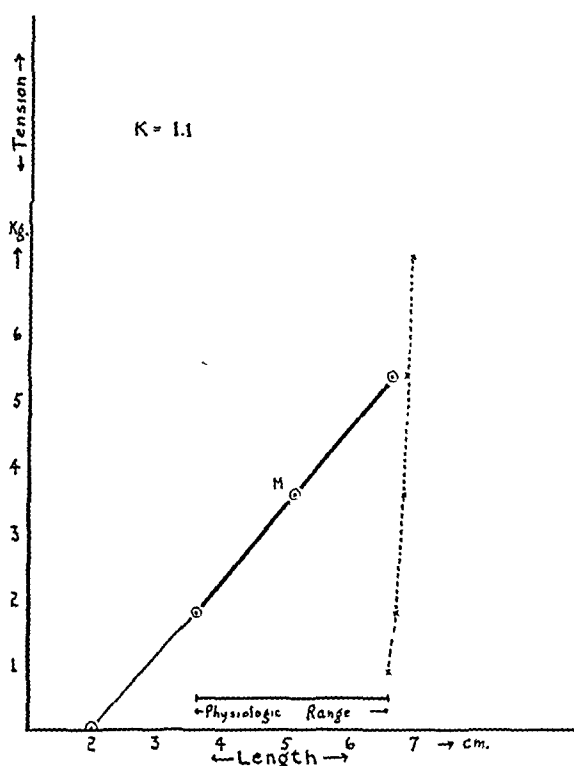


Fig. 3.—Length-tension curve for a typical muscle (dog 17, left tibialis anticus).

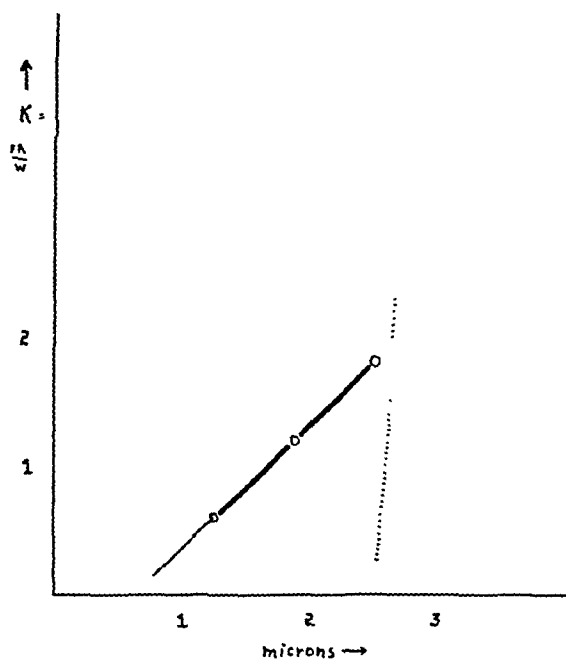


Fig. 4.—(Hypothetic) length-tension curve of a sarcomere.

The following experiments were designed to disclose whether the maximum work done in a physiologic contraction is proportional to the weight of the muscle and to ascertain the value of that proportion.

Full grown, apparently healthy dogs were used. With the animals under barbiturate anesthesia the muscle was exposed, a marker suture inserted into the tendon and its excursion measured as the joint was moved through its physiologic range. The tendon was then divided; a tension scale was clamped to its end, and the tensions developed at various lengths under supramaximal stimulation by an induction coil were measured. In order to obtain isometric values, the muscle length was not allowed to vary during each reading. Readings were taken at both ends and at the midpoint of the physiologic range and at the maximum total shortening. Several readings for the relaxed muscle were taken to show length with varying amounts of passive stretch. When plotted out in a length-tension curve a typical muscle would give a result similar to that seen in figure 3.

An examination of this figure will reveal several interesting facts. The total range of the muscle is from 2 cm.,<sup>4</sup> at which point O tension can be developed, to 6.8 cm., at which point the passive resistance to stretch (charted by the dotted line) mounts exceedingly rapidly. Only about two thirds of this total range, however, is used in life, and it is the optimum two thirds—the part in which maximum tension is developed and yet passive resistance to stretch does not materially interfere. Moreover, even at maximum shortening in life, the muscle still develops quite a respectable tension. This is in accord with previous speculations as to the most reasonable arrangement.

The tension developed at maximum extension in life (5.4 Kg.) is approximately three times that developed at maximal flexion (1.8 Kg.). It will be noted that the "curve" is in reality a straight line. This has been previously remarked by other investigators.<sup>5</sup> Hence the tension at the midpoint of any segment will be equal to the average tension throughout that segment. Since work done = average force  $\times$  distance, it will equal the force at the midpoint of the range, multiplied by the range. If the work in this range is proportional to weight, then  $\frac{F \times R}{W}$  should equal a constant, K, when F = tension developed at midpoint of physiologic range, R = physiologic range and W = muscle weight.

That this relation is valid can be proved, as has been mentioned, either by showing that the physiologic range is always in the same segment of the total length-tension curve or by working out the values for K and finding them constant. Both methods of proof were used.

4. This is not the actual length of the muscle; it represents a reading on the marking tape on which zero was not necessarily opposite the muscles' origin.

5. Steindler, A.: *Mechanics of Normal and Pathological Locomotion in Man*, Springfield, Ill., Charles C. Thomas, Publisher, 1935, chap. 6.

Tables 1 and 2 give the collected data when K was worked out for every muscle tested in 5 dogs. The column headings are self explanatory except, perhaps, "Length with Passive Stretch." This is the length of the unstimulated muscle as stretched by a force which was arbitrarily

TABLE 1.—*Length-Tension Values for Dogs 13, 14, 15 and 16*

Dog	1	2	3	4	5	6	7	8	9	10
			T Maxi- mum	T At	T At	L				
	Physio- logic Range (Cm.)	Maxi- mum Short- ening (Cm.)	Physio- logic Short- ening (Kg.)	Mid- point (Kg.)	Maxi- mum Exten- sion (Kg.)	Passive Stretch	Weight (Gm.)	K	Cross Section of Tendon (Sq. Cm.)	K <sub>T</sub>
13 Tib. ant.....	2.7-4.7	...	...	3.4	...	...	4.9	1.4	.....	.....
Ext. carp. rad....	3.5-4.1	...	3.3	4.3	...	...	4.2	0.6	.....	.....
R. fl. carp. ul.....	2.3-4.5	...	...	2.7	3.6	...	4.0	1.5	.....	.....
14 R. tib. ant.....	1.2-5.0	...	...	3.2	...	...	16.7	0.8	.....	.....
L. tib. ant.....	1.1-4.2	...	...	6.4	...	...	16.1	1.2	.....	.....
L. fl. carp. ul.....	2.2-4.4	0.7	3.6	9.0	...	...	11.9	1.7	.....	.....
L. ext. carp. rad...	2.2-4.4	0.1	...	8.2	...	...	15.1	1.2	.....	.....
15 L. sartorius *.....	11.7-18.2	...	...	1.4	3.2	...	12.4	1.1	.....	.....
L. tib. ant.....	6.0-10.2	4.5	3.6	5.0	7.7	10.5	16.9	1.2	0.044	0.011
L. ext. carp. rad...	10.1-11.5	...	...	>11	...	...	14.6	>1.1	0.093	0.009
R. ext. carp. rad...	9.8-11.5	8.0	...	>11	...	...	15.4	>1.2	0.096	0.011
16 R. sartorius.....	9.0-19.0	...	...	0.9	0.0	19.8	8.8	1.0	.....	.....
L. sartorius.....	13.0-20.0	10.0	...	0.9	...	21.0	7.6	0.8	.....	.....
R. tib. ant.....	4.8-7.7	4.0	...	4.5	...	8.6	10.6	1.3	0.033	0.009
L. tib. ant.....	4.0-7.0	3.0	...	4.5	...	7.8	10.6	1.3	0.036	0.010
L. ext. carp. rad...	6.0-7.5	5.3	...	16.0	...	7.4	9.6	1.7	0.071	0.011

\* All sartorius muscles were dissected free, thus interrupting blood and nerve supply before testing.

TABLE 2.—*Length-Tension Values for Dog 17*

Dog	1	2	3	4	5	6	7	8	9	10
			T Maxi- mum	T At	T At	L				
	Physio- logic Range (Cm.)	Maxi- mum Short- ening (Cm.)	Physio- logic Short- ening (Kg.)	Mid- point (Kg.)	Maxi- mum Exten- sion (Kg.)	Passive Stretch	Weight (Gm.)	K	Cross Section of Tendon (Sq. Cm.)	K <sub>T</sub>
17 R. tib. ant.....	2.8-5.8	2.4	...	3.6	...	6.0	10.8	1.0	0.033	0.009
R. plantaris.....	4.7-6.5	...	3.6	7.2	11.0	6.8	17.6	0.5	0.050	0.008
L. tib. ant.....	3.6-6.6	2.0	1.8	3.6	5.4	6.7	9.9	1.1	0.035	0.011
R. ext. dig. comm.	4.0-5.3	3.5	1.4	3.2	4.5	5.7	3.4	1.2	0.029	0.011

fixed as the force developed by the actively contracted muscle at maximum physiologic shortening. This was used to establish an upper reading for the total range, the lower one being "maximum shortening."

It will be seen that the physiologic range occupies a fairly constant part of the total range (measured between the length at maximum shortening [column 2] and the length with passive stretch [column 6]), being, on the whole, much nearer to the latter than to the former.

K is calculated in column 8. Column 9 represents the cross-sectional area of the tendon obtained by weighing a segment of the tendon and dividing the weight by the length. The specific gravity of tendon was considered to be 1.

If the cross-sectional area of the tendon is proportional to the maximum muscle tension (F) and is substituted for it in the formula  $\frac{FR}{W} = K$  a new value,  $K_T$ , would be obtained. The constancy of this value in column 10 is a check on the accuracy of the muscle tension readings.

TABLE 3.—Length-Tension Values After Lengthening or Shortening of the Tendon or Change in Range

Dog	Physiologic Range (Cm.)	Maximum Total Shortening (Cm.)	Tension at Maximum Shortening (Kg.)	Tension at Mid-point (Kg.)	Tension at Maximum Extension (Kg.)	Length at Passive Stretch (Cm.)	Weight (Gm.)	Weight of Opposite Muscle (Gm.)	K
1 1. R. ext. carp. rad. (tendon length, 2 cm.)	4.5-6.7	4.0	3.6	7.2	11.0	6.5	17.2	21.3	0.92
2. R. ext. carp. uln. (implanted into ulna under tension).....	3.7-3.9	3.6	...	7.3	....	4.4	5.3	7.9	0.3
3. R. tib. anticus (tendon shortened 1 cm.)	5.2-7.5	3.2	4.5	6.8	6.9	9.2	19.2	20.8	0.82
2 4. R. flex. carp. uln. (ulnar head; tendon length, 1.5 cm.).....	2.9-4.3	...	...	...	....	4.6	2.35	4.4	$K_T=0.012$
L. flex. carp. uln.....	1.7-3.3	...	...	...	....	3.6	4.4	....	$K_T=0.012$
5. Rt. ext. carp. rad. (tendon shortened 1 cm.).....	0.8-2.5	-0.3	2.7	6.4	10.0	3.0	10.4	14.7	1.1
3 6. L. ext. carp. rad. (implanted into radius under tension).....	-1.3+1.8	-2.9	2.7	4.5	8.-	2.2	6.6	5.8	1.7
7. L. ext. carp. uln. (tendon lengthened 2 cm.).....	0.5-1.3	0.5	...	3.2	4.5	1.7	2.1	2.6	1.2

In calculating the average K, data on three muscles were omitted—the extensor carpi radialis of dog 13, as its range is obviously wrong (compare flexor) and both extensors carpi radialis of dog 15, which could not be read, as the scale was not graduated beyond 11 Kg. (25 pounds). All remaining values for K were included.

The average K (obtained from seventeen muscles) was 1.2. The average value for  $K_T$  (ten muscles) was 0.01.

Hence, all muscles assign the same portion of their total length-tension curves to the physiologic range. Moreover, at full physiologic extension the tension developed is three times as great as the tension at maximum physiologic shortening.

Where this is not the ideal arrangement (as in the human knee extensors, which are mostly used in a position near the lower end of

their length-tension curve), an apparatus (the patella) to vary the mechanical advantage may be interposed between the tendon and the insertion. If the mechanical advantage is known (cadaver measure-

TABLE 4.—*Length-Tension Values for the Human Quadriceps Ligament*

Degrees	A Distance Moved by Quadriceps, Cm.	B Distance Moved by Foot, Cm.	C Mechanical Advantage A/B*	D Tension Measured at Foot, Pounds	E Tension Devel- oped in Quadri- ceps Ligament, Pounds
180-170	1.1	7	0.15	57	363
170-160	0.8	7	0.11	62	544
150-140	0.6	7	0.085	64	747
140-130	0.6	7	0.085	57	667
110-100	0.5	7	0.071	53	756
100- 90	0.5	7	0.071	55	784
90- 80	0.5	7	0.071	52	728
80- 70	0.5	7	0.071	53	756
60- 50	0.3	7	0.042	49	1,144

\* The distance moved by quadriceps (column A) divided by distance moved by foot (column B) equals the mechanical advantage.

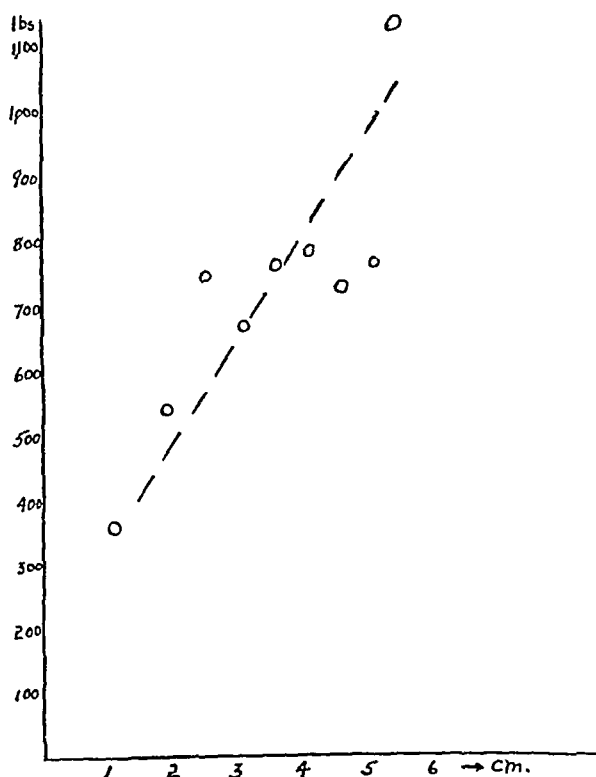


Fig. 5.—Length-tension curve for a human muscle (A. M. A., right quadriceps).

ments, columns A and B, table 4), the actual tension in the quadriceps ligament can be calculated. The length-tension curve thus obtained (chart 5) closely resembles that obtained with the dog preparation.



It may, therefore, be assumed that the maximum work done in the physiologic range makes up a constant portion of the maximum work in the total range and that this work is proportional to the weight of the muscle, that  $\frac{\text{average force (in kilograms)} \times \text{range (in centimeters)}}{\text{weight (in grams)}} = 1.2$ .

The value of this equation in the determination of muscle work and tension is immediately apparent. This equation may be used to determine the tension at resting length (the "absolute muscle power") of an imaginary sartorius muscle which at maximum physiologic extension is 20 cm. long and has a cross-sectional area of 1 sq. cm. By referring to the graphs, it will be seen that it is safe to assume that 20 cm. is not far from the resting length, since passive resistance to stretch begins at or near maximum physiologic extension. By the Weber-Fick law the range will be 10 cm. Substituting in the formula:  $\frac{10 F}{20} = 1.2$ , one finds that  $F = 2.4$  Kg. This is force at the midpoint of range. Force at full extension is always 50 per cent more. Hence, the force at 20 cm. = 3.6 Kg. for a muscle of 1 cm. cross-section. This is exactly the absolute muscle power found experimentally by Recklinghausen. Thus, if one knows only the weight of the muscle, the maximum work done in a physiologic contraction can be calculated. If the range is known in addition, the force at any point in the range can be found.

### 3. EFFECT OF TENDON LENGTHENING, SHORTENING AND TRANS-PLANTATION ON THE RELATION OF THE LENGTH-TENSION CURVE AND THE PHYSIOLOGIC RANGE.

The physiologic range always embraces the same part of the total curve of a normal muscle. The question may arise as to the effect on the length-tension curve of a change in the physiologic range produced by lengthening or shortening a tendon or by transplanting the tendon to a new insertion where the range is different.

Lengthening of a tendon obviously entails a corresponding shortening of the muscle, though the range of excursion remains unchanged. If a tendon were lengthened by an amount equivalent to its physiologic range, its new range would be transposed to a position where the length of the muscle at maximal extension is equivalent to what previously was its length at maximal physiologic shortening. As represented in figure 4 the new range would be from 0 to 1.25, and the muscle at first would be able to exert no power save at the terminal half of its range, and then only to a small extent.

But in life, though this may be true at first, the muscle adapts itself in time to its new range, so that it can exert a fairly large amount of force throughout the whole range. Certainly, this could not have been done by an alteration in the physiology of the sarcomere, permitting it to shorten to more than its previous limit—the physiologic shortening of 1.25 microns brought the sarcomere to one-half its original length

(Weber-Fick law; fig. 4). A further shortening of the same amount would bring it to a length of 0. This is obviously impossible. Moreover, microscopic examination of muscles in which this procedure was carried out (muscle 1, table 3) failed to reveal any detectable difference in the length of the sarcomere as compared with the normal muscle on the opposite side.

The only other possibility is that the muscle fibers have become rearranged inside the muscle, so that this new range of the tendon represents a range which can be included somewhere within the fiber's potentialities. That the muscle fibers do actually rearrange themselves when the range is changed has been noted by various investigators. Roux<sup>6</sup> noted that in the case of a pronator quadratus muscle whose range was contracted by limitation of pronation and supination the fibers had assumed a pennated arrangement. As was shown in section 1 of this paper, this is a modification permitting greater force and shorter range. An infinite number of such modifications are possible. Does the muscle undergo just such a rearrangement as will make the new range take up just the same segment of the total length-tension curve as the old one did? Does this new arrangement once more establish the same relation between the new physiologic range and total range that has been investigated in section 1?

To answer these questions, the following experiments were designed: Three adult dogs were used, and various tendons were lengthened or shortened or had their range changed by aseptic operative procedures. The limb was immobilized in plaster for two weeks (in 1 case for one week), after which the plaster was removed and the animal left to his own devices. All wounds healed by primary union.

After three and a half to four months the animals were reoperated on, and all tendons were found well healed and firmly fixed to their new insertions where transplant had been done. The length-tension curves of these muscles were determined by the procedure used on normal muscles in section 1. The results are summarized in table 3.

Three tendons were lengthened and two shortened, and in two muscles the range was changed. The results may well be analyzed individually.

In dog 1 the right extensor carpi radialis tendon was lengthened 2 cm., which shortened the muscle by almost the amount of its physiologic range. The results, given in table 3, are plotted graphically in fig. 6 and demonstrate that the muscle has so rearranged its internal structure that the physiologic range makes up the same proportion of the total range as it does in normal muscle (compare figs. 3 and 6). More-

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6. Roux, cited by Marey, E. J.: *Des lois de la morphogénie chez les animaux*, Arch. de physiol. norm. et path. 1:88, 1889.

over, the constant  $K$  approaches<sup>7</sup> the value for  $K$  of normal muscle. Clearly the new range represents the same part of each sarcomere's length-tension curve that the old range previously represented. It is noted that the muscle was shortened 2 cm. This is reflected in a diminution of 4.1 Gm. in weight as compared with the corresponding muscle on the opposite side.

The tendon of muscle 2 was implanted into the ulna through a drill hole. Its range previously had been (from the muscle on the opposite side) 1.4 cm., and the muscle thus was reduced to one seventh of its original range. Though maximum total shortening is in correct relation to the physiologic range, passive stretch is a bit high, and  $K$  is low. Apparently adaptation has not become quite complete, owing to the shortness of elapsed time and/or the great change in range.

The right tibialis anticus (muscle 3) showed a result similar to that observed with muscle 1, with excellent adaptation to the new range.

In muscle 4 only slight contraction could be obtained, nor could any be obtained on the opposite side. However, the length with passive stretch (8 pounds; 3.6 Kg.) was in proper relation to the new range. Since  $K$  could not be obtained, the cross-sectional area of a normal segment of its tendon was found and  $K_T$  was calculated. It was found to be 0.012. The opposite muscle is included for comparison.

Muscle 6 showed good adaptation to its new range. The range previously was 1.2 cm. longer. Muscles 5 and 7 showed good adaptation.  $K$  was 1.1 and 1.2 respectively.

These results would seem to indicate that muscle fibers are so arranged that the physiologic range always represents a certain portion of the total length-tension range, and if this relation is disturbed the muscle will rearrange its internal structure to restore it (and enable  $\frac{F}{W}$  to regain its original value when  $F$  is the average force through the new range  $R$ ). This law of adaptation of structure to function represents for muscle what Wolff's law represents for bone. In both cases the internal structure will rearrange itself to fit perfectly an altered function.

It will be seen that the weight of a muscle is peculiarly important in that this and this alone determines the amount of work which can be done in a physiologic contraction. When a muscle is shortened by lengthening of its tendon it is seen to lose weight (cf. muscles 1, 4 and 7, table 3). One would expect the converse of this to be true—that muscles which have been lengthened by tendon shortening should appreciate in weight. Table 3 shows that this was not so in muscles 3 and 5.

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7.  $K$  is low, at 0.92. However, the average  $K$  of three intact muscles on this dog was 0.90. This may be due to the fact that the animal was very old and adaptation slower.

Explanation of this discrepancy seemed difficult until Dr. G. Miyakawa<sup>8</sup> furnished the information, based on experimental work on dog tendons, that tendon shortenings in dogs are uniformly unsuccessful in that the ends become separated and are bridged by fibrous tissue. Hence these muscle bellies were really shortened, and the results at once became consistent with what was to be expected.

However, muscles 2 and 6 were implanted into bone under tension, so that no possibility of separation existed. When this muscle lengthening was accompanied by a great contraction of range (muscle 2) weight diminished, owing perhaps to the difficulty in adaptation to so short a range in the time allotted. On the other hand, when lengthening was not accompanied by a marked change in range (muscle 6) there was a gain in muscle weight over the unlengthened side.

#### 4. IMPLICATIONS

This concept of structural adaptation to function, which may be expressed mathematically as a tendency toward equilibrium at a point where  $\frac{F}{W} \frac{R}{W} = 1.2$ , may aid in the better understanding of certain aspects of muscle physiology and pathophysiology which are frequently met with in orthopedic surgical practice.

*Tendon Lengthening.*—As may be seen from table 3, the muscle whose tendon has been lengthened adapts itself to its new range, and after some time has elapsed the length-tension curve in the new position is identical with that of a normal muscle (fig. 6). However, the weight of muscle tissue is diminished. Since the range remains unchanged and since the value of the fraction  $\frac{F}{W} \frac{R}{W}$  must remain constant, the average force will therefore be diminished in proportion to weight. It is not known whether this diminution in weight, due to shortening of the muscle, is permanent, or whether the muscle belly can elongate again over a period of time by downward growth of fibers on the tendon. This seems doubtful and has not been noticed in repeatedly lengthened human achilles tendons.<sup>9</sup> Consequently, tendon lengthening results in a muscle which, though active throughout its new range, is weakened, probably permanently.

*Tendon Transplantation.*—The transplanted tendon will perfectly adapt itself to its new range, even though it be smaller than the old one.<sup>10</sup> It will be seen (table 3) that if the discrepancy in range is not

8. Miyakawa, G.: Types of Tendon Suture, Master's Thesis, University of Iowa Graduate School, 1939.

9. Steindler, A.: Personal communication to the author.

10. No data are available on the adaptation of parallel-fibered muscles to an increase in range. The muscle fibers would have to grow in length. Subjects in whom the finger flexors have had their range increased, as in Steindler's flexor plastic operation at the elbow, do not accommodate perfectly to their new range, according to a personal communication from Dr. Steindler.

completely out of proportion to the size of the old range, lengthening the muscle by implantation under tension will result in increased muscle weight and therefore in increased muscle power. Hence transplanted muscle should be implanted under moderate tension, provided that it is not great enough for passive overstretching of the muscle beyond physiologic bounds.

*Contractures.*—The contracture of normally innervated flexor muscles (for example) opposed by paralyzed extensors may be regarded as adaptation to change in range. The range is diminished by inability of the extensors to move the joint through a full range of motion. The

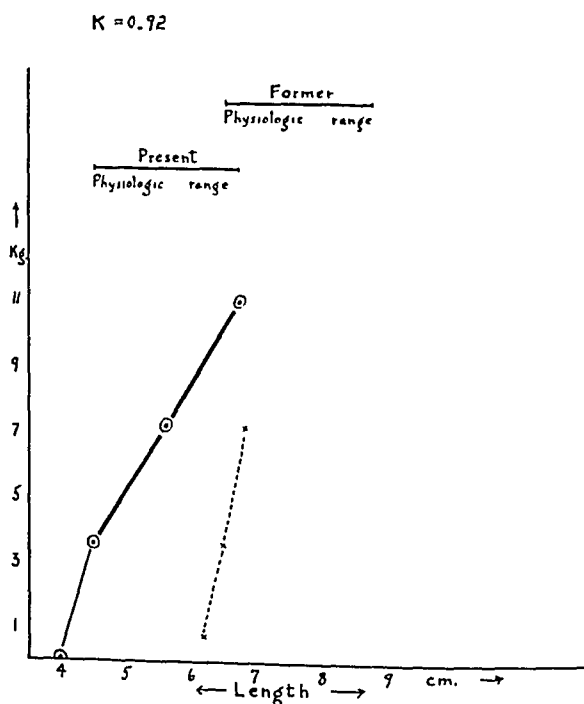


Fig. 6.—Results three and one-half months after lengthening the right extensor carpi radialis tendon in dog 1. See text for explanation.

muscle adapts itself to this new smaller range, and then the process is repeated. As range diminishes (assuming weight to be constant), the average force which can be exerted through that range increases (and passive resistance to stretch also does, maintaining its relative size and position in the length-tension curve). This explains the tremendous resistance to elongation offered by contracted muscles.

If the opponent is not completely paralyzed it seems possible that repeated tendon lengthenings performed on the contracted muscle may diminish its weight to the point where its developed tension no longer exceeds that of its antagonist and equilibrium is attained. Indeed, if the discrepancy in strength is slight, especially if the muscles are under

innervational overload (as is frequently the case in spastic persons), a single tendon lengthening may weaken a muscle enough to swing the balance in the other direction and cause a contracture of the previously elongated side.

*Methods of Increasing Muscle Power.*—A consideration of the formula will show the futility of attempting to increase muscle power by transplanting its tendon to a new site designed to increase its mechanical advantage. Transplant of the biceps insertion, for instance, to twice its original distance from the center of motion at the elbow joint will double its range and mechanical advantage (disregarding motion at the shoulder). But, unfortunately, as it adapts<sup>11</sup> itself to this new doubled range, the average tension it can exhibit will necessarily diminish to one-half the original average tension, since the work done in a contraction must remain proportional to the weight (which presumably does not change). Hence in a short time conditions are right back where they started from. The only way to increase the amount of work done in a contraction is to increase the weight of the muscle. An instance of the truth of this concept is seen in the example afforded by congenital coxa vara, with which the mechanical advantage may actually be increased owing to the greater perpendicular distance between the line of action of the abductors and the center of motion at the hip. Yet abduction is weak, owing to shortening (and consequent decrease in weight) of the muscles.

One sees that the only way to increase muscle force is to increase the weight or decrease the range. Attempts to increase the weight (and therefore the average force) of a muscle by lengthening it by shortening its tendon have not been conclusive in experiments on dogs, owing to technical difficulties. Further investigations are needed to show whether this is practicable, especially in the partially paralyzed muscle, where a limited nerve supply may entail an absolutely limited weight of muscle tissue.

However, an example in which the other type of approach (decreasing the range) was successful is seen in muscle 6, table 3. This muscle's range was shortened, but in return it gained 1.3 Kg. in maximum tension developed over its unchanged mate on the opposite side (tension on the right, not shown in the diagram, 6.8 Kg.).

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11. Assuming that the biceps could grow in length sufficiently so that its fibers could attain a length double the range. It is not known whether this occurs. It is only fair to state that if no adaptation to a longer range is possible the work done in a contraction theoretically may increase, despite the fact that there is no change in weight, owing to the expansion of the range to include the hitherto unused part of the length-tension curve (below ordinate 0.6 in chart 4).

Moreover, the average tension of muscle 2 (7.3 Kg.) was more than twice the average tension of the normal muscle on the opposite side (3.6 Kg.) despite a decrease in weight.

It would seem that a more practicable method of increasing the strength of a partially paralyzed muscle would be to sacrifice range for power, for example, by a bone block designed to limit motion at a joint to a range no more than absolutely necessary. After the muscle had become contracted (since that is what it amounts to) to its new range, its force would be increased to the same degree that its range had been decreased.

It is realized that these last few paragraphs are necessarily somewhat speculative, but the conclusions follow logically from the experimental results, and they open a new and important field for investigation. It is hoped that further clarification will soon be forthcoming.

#### SUMMARY AND CONCLUSIONS

The Weber-Fick law is reaffirmed. The physiologic contraction represents a shortening of the fiber length by one half.

The physiologic range bears a constant relation to the total length-tension curve.

The maximum tension developed at maximum physiologic length is three times that developed at maximum physiologic shortening.

The work done in the physiologic range is proportional to the weight of muscle tissue.

The value of this proportion as obtained in the experimental preparation may be expressed as follows:

$$\frac{F \text{ (average force in kilograms)} \times R \text{ (range in centimeters)}}{W \text{ (weight in grams)}} = 1.2$$

Muscle structure tends to adapt itself to any change in function (at least so far as shortening of the muscle belly or contraction of range is concerned), so that the foregoing five postulates are always satisfied.

The practical implications of these conclusions are suggested.

The value for "absolute muscle power" obtained by von Recklinghausen (3.6 Kg. per square centimeter) is corroborated.

Drs. Joel Hartley and Irving Redler aided in the experimental work. Dr. Knowlton, of the department of physiology, and Mr. Shelley, of the department of physics, gave advice and criticism.

This investigation was suggested by the teaching of Dr. Arthur Steindler.

# CRANIAL CHORDOMAS

## A CLINICAL AND PATHOLOGIC STUDY

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The term chordoma refers to a neoplasm arising from embryonic rests of the chorda dorsalis or notochord, which in its development more or less reproduces the structure of the primitive notochord. Chordomas arise in the craniospinal axis in certain definite locations, the selection of which can be explained on an embryologic basis. While they rarely metastasize, the clinical course is characterized by slow expansile enlargement with destruction of adjacent bone and compression of neural structures and by recurrences after operation.

### EMBRYOLOGY

The embryology of the chorda dorsalis has been reviewed by others<sup>1</sup> and will be given briefly here. The notochord forms the primitive axial skeleton of all vertebrates, and in certain lower forms, such as the *Amphioxus*, it forms the sole axial skeleton. The structure is formed primarily by the proliferation of cells from the anterior end of the primitive streak. While some writers consider the chorda to be of entodermal origin, it comes to lie between the ectoderm and the mesoderm and may be looked on as a mesodermal derivative.

A narrow cord of cells, known as the head process, differentiates early and wedges itself between the entodermal cells, forming a portion of the wall of the entodermal cavity. In the process of development, the notochord extends as far forward as the pharyngeal membrane but the final anterior extremity is marked by the sella turcica of the sphenoid bone. As the notochord pierces the occipital portion of the skull it makes an S-shaped curve. Hass<sup>2</sup> has pointed out that the structure, lying in the midsagittal plane, comes to lie near the dorsal surface

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1. Williams, L. W.: Later Development of the Notochord in Mammals, *Am. J. Anat.* 8:251, 1908.

2. Hass, G. M.: Chordomas of Cranium and Cervical Portion of the Spine: Review of the Literature with Report of Case, *Arch. Neurol. & Psychiat.* 32:300-327 (Aug.) 1934.



of the cartilage at three points: (1) in the hypophysial fossa; (2) a short distance caudal to the fossa, and (3) anterior to the foramen magnum (fig. 1).

In the process of development, the anterior end of the chorda is projected forward to lie between the perichondrium and the cartilage of the dorsum sellae. The middle portion comes to lie between the cartilaginous occipital plate and the dorsal wall of the pharynx. It is this middle portion which presents many irregularities and is frequently embedded in the retropharyngeal tissue (fig. 2). The position of the notochord on the dorsal wall of the pharynx has led to the suggestion that some of the tumors which form here are due to proliferation of remnants of the pharyngeal portion.

As the chorda separates from its attachments in the distal portions, it becomes surrounded by a secondary mesodermal layer which eventually becomes the adult vertebrae. In the process of condensation, that portion in the vertebral bodies becomes partially forced into the intervertebral disks, where it takes part in the formation of the nucleus pulposus. Thus, while the notochord itself disappears, remnants of it may persist in the intervertebral disks.

The apical odontoid ligament, which also is formed by mesodermal elements, is traversed by the chorda, and remnants may also persist here. Posteriorly, it can be traced through the anterior arch of the atlas.

#### LITERATURE

There have been few attempts to classify the chordomas other than topographically, although it is evident that certain of the tumors appear clinically and histologically more malignant than others. Coenen's<sup>3</sup> classification has been most satisfactory and is given here, slightly modified:

- I. Cranial
  - A. *Ecchordosis physalifera* (clivus)
  - B. Chordomas
    - 1. Sphenoid
    - 2. Spheno-occipital (clivus)
    - 3. Nasopharyngeal
    - 4. Dental (including maxillary and mandibular)
- II. Vertebral
  - A. Cervical (including those arising from the odontoid process of the second cervical vertebra)
  - B. Thoracic
  - C. Lumbar
- III. Sacrococcygeal (caudal)
  - A. Antesacral
  - B. Central
  - C. Retrosacral

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3. Coenen, H.: *Das Chordom*, Beitr. z. klin. Chir. **133**:1-77, 1925.

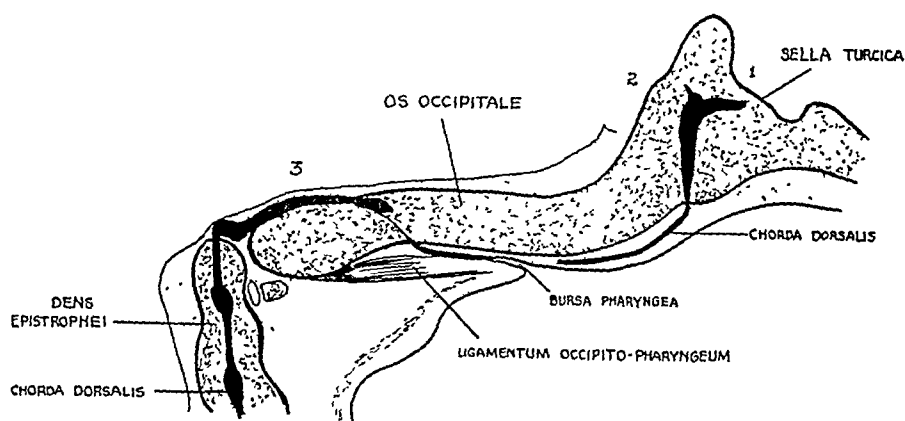


Fig. 1.—Drawing to indicate the course of the chorda dorsalis through the odontoid process and foramen magnum, its passage through the clivus and the relation of the chorda to the pharyngeal wall and occipital bone. (Redrawn from Fischel, A.: *Lehrbuch der Entwicklung des Menschen*, Berlin, Julius Springer, 1929.)

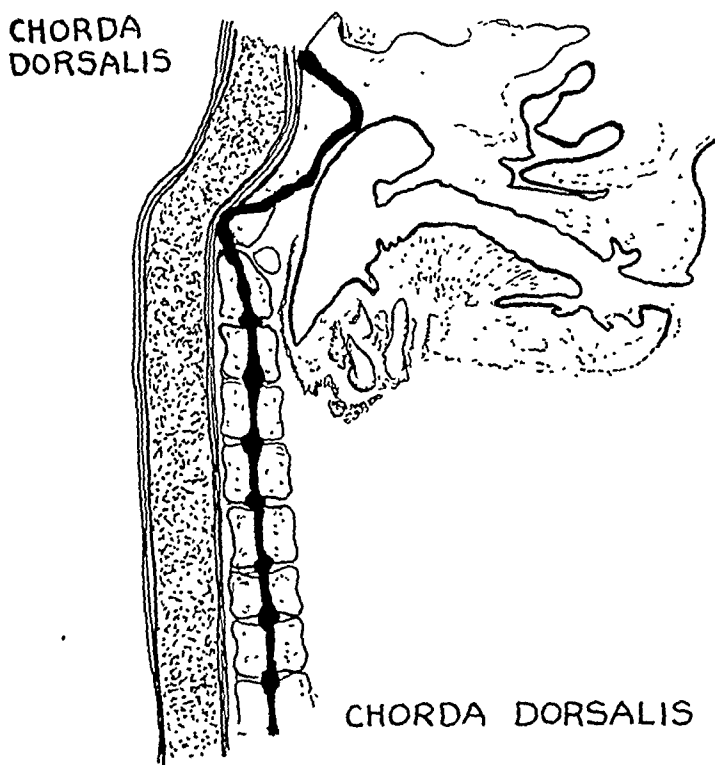


Fig. 2.—Detailed drawing to indicate the upper course of the chorda dorsalis. Note the devious passage through the occipital bone, the relation of the chorda to the pharyngeal bursa. (Redrawn from Linck, A., and Warstat: *Beitr. z. klin. Chir.* 127:612-626, 1922.)

In 1856 Virchow noted a small, slimy excrescence on the clivus. In 1857 he gave it the name of *ecchondrosis physaliphora spheno-occipitalis*.<sup>4</sup> Müller,<sup>5</sup> in 1858, was the first to point out that the structure was the cephalic remnant of the notochord, a fact which was substantiated in 1895 by the experimental work of Ribbert.<sup>6</sup> This structure is said to be noted at from 1.5 to 2 per cent of autopsies.<sup>7</sup>

The so-called "benign chordomas," described as originating from the clivus, do not belong to the neoplastic group and actually represent chordal ectopia. These are small, mushroom-like tumors varying from 1 mm. to 3 cm. in size. They are well circumscribed, soft, semitranslucent and generally milky white. They are attached to the midline by a small stalk which perforates the dura and are usually observed incidentally at autopsy. An excellent example has been described by Van Wagenen.<sup>8</sup>

The invasive and malignant growths are often large, compressing the adjacent neural tissue, enveloping nerves and invading and destroying the contiguous bony structures. The tissue is poorly vascularized, but the tumor is apt to have a reddish brown color due to interstitial hemorrhage. The well circumscribed appearance of the growth belies the microscopic appearance and clinical behavior.

The most common intracranial location is at the spheno-occipital synchondrosis. Originating from the clivus, these tumors are essentially in the midline at first but extend widely in all directions. They may be associated with a variable degree of destruction of the basilar process of the occipital bone. On the roentgenogram this may be revealed as a V-shaped notch in the basilar plate, or it may be represented by evidence of destruction of bone. Anterior extension may be sufficient to involve the parasellar structures. Occasional cases have been reported in which there was extension into the anterior fossa. Ventrally, the growth of the tumor may be sufficient to involve the nasopharynx, maxillary sinus and posterior choanae. The primary involvement is of the pons and medulla, where the characteristic cranial nerve palsies may give rise to severe clinical symptoms.

4. Virchow, R.: Untersuchungen über die Entwicklung des Schädelgrundes im gesunden und krankhaften Zustande und über den Einfluss derselben auf Schädelform, Gesichtsbildung und Gehirnbau, Berlin, Georg Reimer, 1857, p. 51.

5. Müller, H.: Ueber das Vorkommen von Resten der Chorda dorsalis bei Menschen nach der Geburt und über die Verhältnisse zu den Gallertgeschwülsten an Clivus, Ztschr. f. rat. Med. **2**:202-229, 1858.

6. Ribbert, H.: Ueber die experimentelle Erzeugung einer Ecchordosis physaliphora, Verhandl. d. Kong. f. inn. Med. **13**:455-464, 1895.

7. Stewart, M. J., and Morin, J. E.: Chordoma: A Review with Report of a New Sacrococcygeal Case, J. Path. & Bact. **29**:41-60 (Jan.) 1926. Ribbert.<sup>6</sup>

8. Van Wagenen, W. P.: Chordoblastoma of the Basilar Plate of the Skull and Ecchordosis Physaliphora Spheno-Occipitalis: Suggestions for Diagnosis and Surgical Treatment, Arch. Neurol. & Psychiat. **34**:548-563 (Sept.) 1935.

Occasional cases have been recorded in which the growth arose from the body of the sphenoid. Such an unusual instance was described by Adson, Kernohan and Woltman,<sup>9</sup> in which the tumor arose from the body of the sphenoid bone, compressed the left optic nerve and extended into the middle cranial fossa. Tumors arising from the anterior extension of the chorda encroach on the sella and suprasellar structures and simulate the usual tumors arising in this region.<sup>10</sup>

With the exception of those tumors originating in the sacrococcygeal region, the vertebral chordomas are uncommon. In the sacrococcygeal region these tumors may cause widespread destruction of the bony tissues, though in some cases roentgen examination may show no abnormality. Fletcher, Woltman and Adson<sup>11</sup> have emphasized the importance of exploring the sacral hollow on digital rectal examination. In 9 of their 10 cases of sacrococcygeal chordoma the tumors were disclosed in this manner.

Of the remaining vertebral axis, the cervical region is most commonly involved. Here the tumors may appear in any region from the atlas to the sixth cervical vertebra. Those high in the cervical region may involve the retropharyngeal space by anterior extension, and in some instances the tumor has been palpable in the posterior triangle of the neck. Origin from the odontoid ligament is difficult to prove, because of involvement of the adjacent structures, but it probably occurs.

Origin of the growth in the thoracic and lumbar regions is most rare. Hutton and Young<sup>12</sup> have reported a case in which there were erosion of the fourth, fifth and sixth thoracic vertebrae and compression of the spinal cord. Zollinger<sup>13</sup> reported a case in which operation was done by Cutler and in which the tumor extended from the first lumbar vertebra to the sacral region, apparently arising from the body of the vertebrae.

#### REPORT OF CASES

CASE 1.—The patient was a 35 year old woman who was admitted to the Cleveland Clinic Hospital with the chief complaint of pain in the head, present for about two years. It had been generalized but was most marked over the

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9. Adson, A. W.; Kernohan, J. W., and Woltman, H. W.: Cranial and Cervical Chordomas: Clinical and Histologic Study, *Arch. Neurol. & Psychiat.* **33**:247-261 (Feb.) 1935.

10. Bailey, P., and Bagdasar, D.: Intracranial Chordoblastoma, *Am. J. Path.* **5**:439-450 (Sept.) 1929.

11. Fletcher, E. M.; Woltman, H. W., and Adson, A. W.: Sacrococcygeal Chordomas: Clinical and Pathologic Study, *Arch. Neurol. & Psychiat.* **33**:283-299 (Feb.) 1935.

12. Hutton, A. J., and Young, A.: Chordoma: Report of Two Cases; a Malignant Sacrococcygeal Chordoma and Chordoma of the Dorsal Spine, *Surg., Gynec. & Obst.* **48**:333-344 (March) 1929.

13. Zollinger, R.: Chordoma of the Third Lumbar Vertebra: Report of Case, *Am. J. Surg.* **19**:137-139 (Jan.) 1933.

vertex, with some radiation to the occiput and the temporal regions. The pain was "pressure-like," was usually dull but at times severe and was occasionally associated with nausea and vomiting. Some time after the onset of the pain there had been noted decreased visual acuity in the left eye.

Eight months before admission the patient noticed inability to rotate the left eye outward. Three months later she awoke one morning to find that she was unable to open the left eye. When the lids were separated with the fingers, a complete paralysis of all movements of the globe was present. She had some associated blurring in the right eye and complained of numbness over the left side of the face. There had been progressive increase in the severity of the headaches and more frequent episodes of nausea and vomiting. Memory had failed slightly, but there had been no symptoms referable to the ear and no difficulty in speaking.

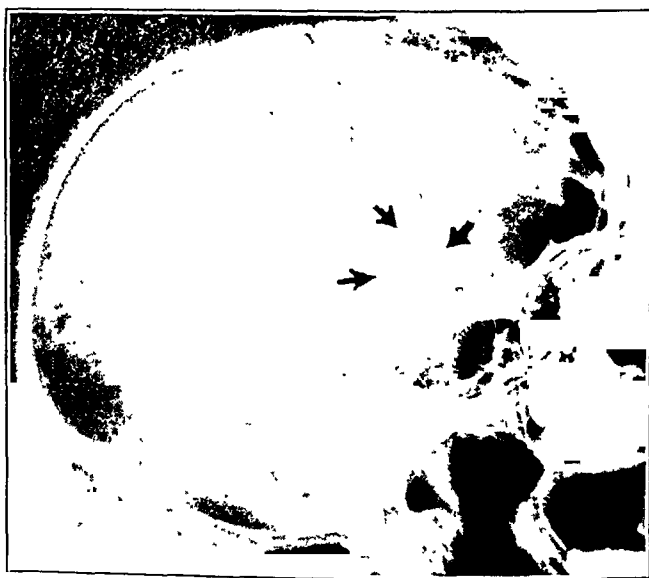


Fig. 3 (case 1).—Roentgenogram to illustrate the calcification within the tumor extension in the left temporal region.

Examination revealed complete ptosis of the left eyelid and complete external ophthalmoplegia. The left pupil measured 3 mm. in diameter as compared to 4 mm. for the right, and did not react to light or in accommodation. There was mild edema of the optic disks, with slight pallor on the nasal side of the disk. Vision was 6/12 on the right, but on the left the patient was barely able to count fingers at a distance of 6 inches (15 cm.). Vision in the left eye was limited to the nasal field, and that in the right eye was concentrically contracted, slightly more on the temporal than on the nasal side.

The reflexes were active and equal, and pathologic reflexes were absent, as were cerebellar signs. Roentgen examination disclosed some erosion of the posterior clinoid processes and calcific deposits outlining a large tumor in the left temporal region. The growth had apparently caused some erosion of the left sphenoid ridge (fig. 3).

The clinical diagnosis was tumor in the left temporal region, possibly meningioma of the sphenoid ridge.

*Operation.*—At operation the gyri of the temporal lobe were found to be distorted and the sylvian fissure dislocated upward. A firm growth could be palpated just beneath the cortex. After incision of the cortex a smooth encapsulated tumor was found 1 cm. from the surface of the brain. Incision into the capsule of the tumor was followed by the extrusion of considerable gelatinous material. After removal of the contents of the tumor with the curet and suction, the shell of the growth was freed from the temporal lobe and the growth found to be completely extradural. It had filled the entire middle fossa, and an extension about 2 cm. in width crossed the tip of the petrous bone to a point of attachment on the posterior surface of the basilar bone. This portion was firmly adherent and could not be removed. After removal of the wall of the tumor, the fifth nerve and the gasserian ganglion were exposed and were found to have been dislocated laterally.

Convalescence from this procedure was quite satisfactory, and the patient was discharged on the fourteenth postoperative day. When seen again, five weeks after operation, she felt quite well but still had complete paralysis of the third, fourth and sixth cranial nerves on the left. Thirteen months after operation she reported that she was feeling fine and that she could now open the left eye but could not rotate it outward.

*Pathologic Picture.*—The tumor was a chordoma in which extensive degeneration, hyalinization and calcification had taken place to alter the general appearance so typical of this type of growth.

The largest portion of the tumor consisted of deeply basophilic matrix in which were scattered elongated polygonal cells which contained pyknotic nuclei and a moderate amount of finely granular, eosinophilic cytoplasm with indistinct boundaries. The great majority of the cells appeared to be in various stages of degeneration, although scattered nests of typical "foam" cells could be observed. These contained many vacuoles, which caused an eccentric position of the nuclei. In other places vacuolation of the cells was sufficient so that nuclei were not apparent.

Elsewhere, the tumor tissue appeared to have been the site of extensive hyalinization and replacement with fibrous tissue. Again, scattered nests of degenerated and ill defined physaliferous cells could be observed.

There were areas of marked calcification, occurring in some places as solid masses and elsewhere as scattered foci. Throughout the tumor, tissue could be observed which represented portions of the fibrous trabeculae which traversed the growth to form irregular lobules. The tissue was poorly vascularized, with small, thin-walled vessels confined to the stroma.

*Comment.*—In this instance, although the tumor had apparently originated from the posterior surface of the basilar bone, the greatest portion had extended anteriorly and laterally to involve the structures of the middle fossa. Calcification within a chordoma is unusual, particularly when it is of sufficient amount to outline the growth roentgenographically.

The cranial nerve palsies, so characteristic of the intracranial chordomas, are easily explainable by the location of the larger portion of the tumor. Hass<sup>2</sup> has pointed out that paresis of the abducens nerve often precedes paralysis of the other ocular nerves.

CASE 2.—The patient was a 38 year old woman who at the time of her admission to the Cleveland Clinic Hospital was confused, disoriented and dysarthric. The history, obtained from relatives, was that for many years and perhaps for all her life the patient had had an internal strabismus. Six months prior to admission she began to complain of pain in the left leg and arm, and six weeks before admission she gradually began to lose strength in the left leg and to a lesser extent in the left arm. About three weeks later she suddenly noticed deafness in the left ear and paralysis of the left side of the face, associated with numbness. At this time her speech became unintelligible and she had difficulty in swallowing, choking with either solid or liquid food. She was emaciated and had lost 35 pounds (16 Kg.) during the six months preceding hospitalization.

Examination disclosed marked impairment of sensation in the left side of the face, with some ulceration of the left cornea. There was complete paralysis of the left sixth, seventh and eighth nerves. The optic disks were normal in appearance. The ninth and tenth nerves could not be tested satisfactorily, but there appeared to be some paralysis of the left vocal cord. The sternocleidomastoid muscle on the left seemed to be weak. The tongue was atrophied on the left and deviated to that side on protrusion.

Caloric stimulation of the left ear gave no response; the response from the right was active. There was pronounced weakness of the left arm and leg, with a positive Babinski sign on the left. The tendon reflexes were normal; the abdominal reflexes were absent.

The spinal fluid pressure was 140 mm. of water. The fluid contained no cells; the Pandy reaction was negative, as were the Wassermann reaction and the colloidal gold curve. The total protein content of the spinal fluid was 40 mg. per hundred cubic centimeters. Roentgen examination of the skull disclosed no abnormality. There was no evidence of tumor in the nasopharynx on visual and digital examination.

The clinical diagnosis was tumor in the left cerebellopontile angle.

*Operation.*—A left cerebellar craniotomy disclosed the seventh, eighth, ninth, tenth and eleventh nerves to be tightly stretched over the lateral surface of a smooth, round bluish encapsulated tumor which lay beneath the pons. No fluid was obtained on aspiration of the growth. An incision was made into the capsule at a point between the nerves which led through the jugular foramen and those which led through the acoustic foramen. The contents consisted of a semisolid, hyaloid and rather translucent material, which was easily removable. A large quantity was removed with the curet and aspirator until there was little left of the tumor but a very thin capsule. This separated readily from the cranial nerves and the anterior surface of the pons but was firmly attached to the basilar bone. The free portion of the capsule was removed, and the portion adherent to the basilar bone was treated with the electrocautery.

There was rapid improvement in the patient's condition after operation. The speech became quite distinct, and the mental confusion disappeared. The patient was discharged on the fourteenth postoperative day. When she was seen again, four months later, the hemiparesis had disappeared and the cranial nerve palsies had recovered, with the exception of that referable to the sixth nerve. There appeared to be some weakness of the left side of the soft palate, and although the tongue protruded in the midline the left side of it was still atrophied.

*Pathologic Picture.*—The tumor was enclosed in a thin, relatively avascular capsule of fibrous tissue which was continuous with the septal strands which

divided the tumor into irregular lobules. The tumor tissue was formed by cords, masses and strands of epithelioid cells embedded in an avascular, abundant matrix (fig. 4 *A*).

The individual cells were irregularly polygonal and for the most part had well defined boundaries, although in scattered areas the cytoplasmic outlines were not distinct. The cytoplasm took the eosin stain well and was highly vacuolated. In most instances there were many vacuoles in each cell, giving a fibrous, stringy or "foamy" appearance. An occasional cell was seen in which a few or no vacuoles were present, and in these the cytoplasm appeared finely granular (fig. 4 *B*).

The nuclei were relatively small, compact and chromophilic. They were slightly elongated and generally situated eccentrically within the cell. In some cells the

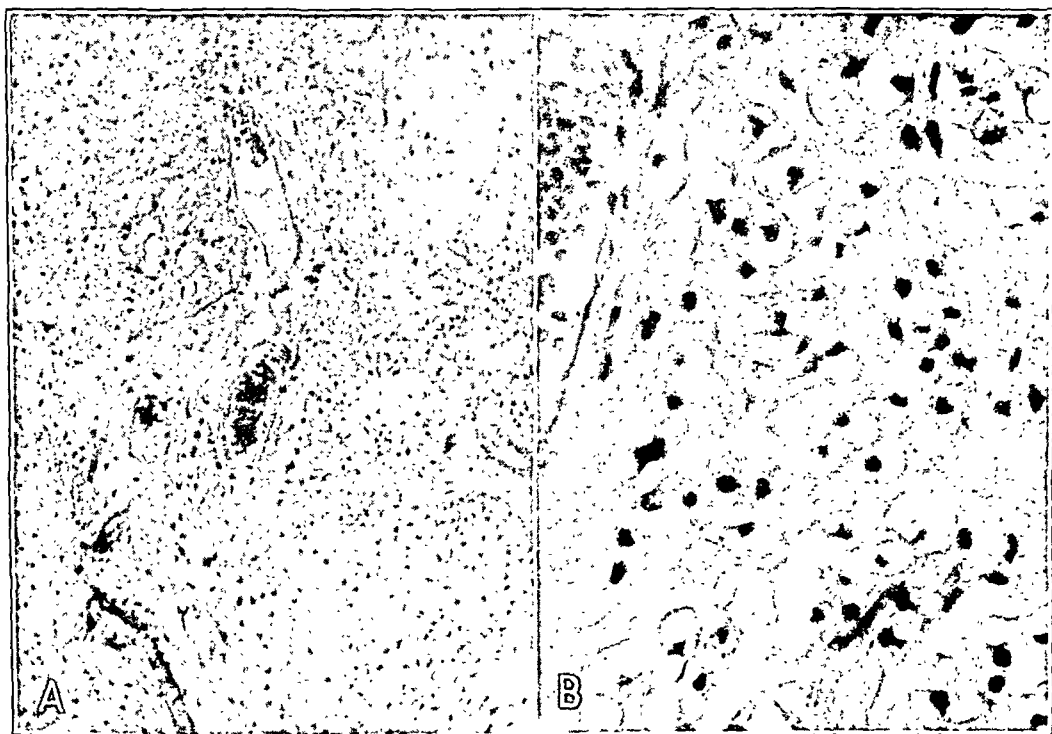


Fig. 4 (case 2).—*A*, photomicrograph of the tumor. Note the vacuolated cells within the homogeneous matrix, the interlobular connective tissue and the thin-walled vessels. *B*, photomicrograph to illustrate the detailed cell structure. Note the multiple vacuoles within the cytoplasm and the "fibrous" appearance of the cytoplasm.

nucleus was displaced to the periphery, giving a "signet-ring" appearance. No mitotic figures were observed, and no vacuolation of the nuclei was evident.

The matrix was more abundant in the central portion of the lobules, where it appeared homogeneous and basophilic. At the periphery the cells were more closely applied and tended toward a cordlike arrangement. Occasional foci of degeneration were observed, wherein the matrix appeared stringy and contained fibrils. There were many typical physaliferous cells which contained a central cytoplasmic mass with radiating fibrils across a clear zone to the protoplasmic boundary. No multinucleated or giant forms were observed.



The blood vessels of the tumor were confined to the fibrous tissue partitions and were thin walled and small. Occasional areas of interstitial hemorrhage were present, limited for the most part to the fibrous spaces between the lobules. Special stains disclosed the presence of large amounts of mucin within the tumor tissue.

*Comment.*—Although the tumor typically originated in the midline beneath the pons, this case again illustrates the tendency toward unilateral involvement of the cranial nerves. It is somewhat unusual for a tumor of this size to affect the cranial nerves—by pressure alone, since the growths are apt to incorporate the nerves within them in the process of extension. The fact that this is not invariably true, however, increases the chances of operability. In the second case reported by Bailey and Bagdasar,<sup>10</sup> in which the patient was operated on by the transsphenoidal route, there were compression and elongation of the third, fourth and sixth cranial nerves by a large, friable tumor mass situated between the infundibulum and the pons. In Hass' <sup>2</sup> case, however, there was involvement of the cranial nerves by a large tumor which incorporated practically all the nerves from the sixth down.

CASE 3.—The patient was a 22 year old woman who was first seen at the Cleveland Clinic with the complaints of diplopia, internal strabismus of the right eye, headaches, change in the voice and difficulty in swallowing.

Two years prior to examination the patient first noted occasional diplopia on right lateral gaze, associated with a tendency toward internal deviation of the right eye. These symptoms became more marked and had been constant for about six months prior to examination. During this time she had frequently choked on attempts to swallow solid food. For the last few months there had been a lowered pitch to the voice, with inability to speak loudly. For a month before coming to the clinic she had been subject to dizzy spells in which there was a tendency for objects to appear as if they were swaying. The patient had lost 30 pounds (13.6 Kg.) in several months.

Examination disclosed no cerebellar signs. The optic disks and visual fields were normal. The corneal reflexes were sluggish, and there were hypesthesia and hypalgesia in the cutaneous distribution of the second and third divisions of the right fifth nerve. There was complete palsy of the right sixth nerve but no facial weakness. The right side of the pharynx was anesthetic, and some impairment of sensation was present over the right side of the soft palate. The sense of taste over the posterior third of the right side of the tongue was also impaired. The uvula retracted to the left, and the voice was husky. The right vocal cord was fixed in the cadaveric position. The right sternocleidomastoid muscle was atrophic and weak, and the right trapezius muscle was likewise involved. There was atrophy of the right side of the tongue, which deviated to that side on protrusion.

The deep and superficial reflexes were generally diminished; there were no pathologic reflexes. No myotactic irritability was demonstrable, although, according to the patient's description, she had experienced fibrillations of the muscles of the forearms and thighs. There was a decided bulge to the right lateral wall of the nasopharynx. A roentgenogram of the skull disclosed no abnormality.

The clinical diagnosis was malignant tumor of the nasopharynx with intracranial extension through the basilar bone.

The patient was not seen again until about four months later, at which time, in addition to the aforementioned symptoms, there were some nystagmus on lateral gaze, absent abdominal reflexes and a positive Babinski response on the right.

A right cerebellar craniotomy was done. After incision of the pontile cistern it was possible to elevate the cerebellar lobe and expose the smooth, gray capsule of a large tumor which apparently took origin from the basilar bone anterior and medial to the jugular foramen. The ninth, tenth and eleventh cranial nerves were stretched tightly over the outer aspect of the growth, which approached within 2 mm. of the seventh and eighth nerves but did not displace them. The capsule of the tumor was almost avascular, and it was possible to remove the pinkish gray, soft and almost mucoid contents. The tumor was approximately 6 cm. in length and 4 to 5 cm. in width, reaching almost to the opposite jugular



Fig. 5 (case 3).—Photograph of the base of the skull after removal of the brain. Note the constriction in the tumor (which indicates the supratentorial extension) and the smooth, encapsulated dorsal surface of the growth.

foramen. The fifth and twelfth cranial nerves were not visualized. The tumor had eroded entirely through the basilar bone at the point of attachment over an area about 2 cm. in diameter. The capsule posterior and medial to the internal auditory meatus was of bony hardness. The only troublesome bleeding occurred from a point within the capsule at the site of attachment, the tumor being otherwise relatively avascular. It was necessary to sacrifice the ninth and tenth nerves to control this bleeding, which was coming from a point in the opening in the bone, apparently from the posterior pharyngeal arteries.

The patient recovered satisfactorily from the operation, and when she was next seen, about nine months later, there appeared to be some return of function in the eleventh and twelfth cranial nerves. There were moderate dilatation of the right pupil and beginning right hemiparesis. It was felt at this time that the tumor was recurring. The patient gradually failed. She died ten months later.

*Pathologic Picture.*—At autopsy the significant positive abnormalities were limited to the head. Arising from the spheno-occipital synchondrosis, extending anteriorly under the tentorium and infiltrating the right temporal bone and the greater wing of the right sphenoid bone was a large growth which was entirely extradural. The tumor was lateral to the sella turcica and in one portion extended downward to the roof of the nasopharynx. The branches and ganglion of the fifth cranial nerve were stretched tightly over the surface of the tumor, which was firm and slightly fluctuant. The posterior extension passing beneath the tentorium was yellow and gelatinous, while the extension toward the roof of the nasopharynx was firm and white and had a glistening cut surface.

There was no point of attachment or infiltration of the brain. The portion in the posterior fossa crossed to the left and produced a marked indentation in the left side of the pons and the left cerebral peduncle and cerebellum, while the supratentorial portion had compressed the right temporal lobe on its medial aspect (fig. 5).

Microscopic examination revealed a typical chordoma. There was a well developed capsule of fibrous tissue, which was continuous with the septal strands which divided the tumor into characteristic lobules. The tumor tissue was composed of large, epithelioid cells containing several large or numerous small vacuoles. The tissue gave a positive staining reaction for mucin. The nuclei varied in size and position but were generally compact and centrally placed. The growth was moderately avascular, but there was considerable interstitial hemorrhage. There were no giant cells, and mitotic figures were few. The matrix was homogeneous and basophilic.

*Comment.*—This case illustrates the ease with which chordomas which involve or extend into the nasopharynx may be confused with primary nasopharyngeal growths. Nasopharyngeal extension of an intracranial chordoma occurs infrequently, probably because the marked cranial nerve palsies call attention to the growth before this has occurred. Hass,<sup>2</sup> however, cited the case observed by Arauz and Podesta,<sup>14</sup> in which the symptoms of nasopharyngeal obstruction were present for twelve years before signs of intracranial involvement were evident. It should be noted that nasopharyngeal extension is more common with the growths arising in the cervical portion of the spine (Syme and Cappell;<sup>15</sup> Adson, Kernohan and Woltman<sup>9</sup>), the tumors originating in the anterior extremity of the chorda dorsalis (Bailey and Bagdasar<sup>10</sup>) and the very rare growths arising from the odontoid process. However, nasopharyngeal extension is fairly typical if the spheno-occipital growths are allowed to progress to that point. This is preceded, of course, by destruction of the basiocciput, although it has been pointed out that the extent or volume of the nasopharyngeal portion may not parallel that of the intracranial lesion.<sup>2</sup>

14. Arauz, S. L., and Podesta, R.: *Cordomas malignas del cavum*, Prensa méd. argent. **10**:461, 1923-1924.

15. Syme, W. S., and Cappell, D. F.: *Chordoma of Cervical Vertebrae with Involvement of the Pharynx*, J. Laryng. & Otol. **41**:209-222 (April) 1926.

# Major Clinical Features in Three Cases of Chordoma

Case	Patient's Age and Sex	Duration of Symptoms	Cranial Nerve Involvement	Motor System	Sensory System	Convulsions	Nasopharyngeal Extension		Cerebellar Signs	Visual Field Defect	Operative Picture	Roentgen Picture	Result	Autopsy
1	35 F	2 years	II, III, IV, VI	..	..	..	..	..	.....	Hemianopia	Extradural left temporal tumor, attached to posterior surface of basilar bone	Calcified I. temporal tumor	Improved	
2	38 F	? (at least 6 mo)	All nerves to XII on left	Left hemiparesis	..	..	..	..	..	..	Tumor under pons, attached to basilar bone; extension to the left, stretching cranial nerves	..	Improved	
3	22 F	2 years	V, VI, IX, X, XI, XII	.	.	.	Bulge of right wall	.	.	.	Tumor originating from basilar bone, both sides; stretching of right nerves; perforation of basilar plate	..	Improved, died from recurrence 20 months after operation	Tumor in nasopharynx, posterior and middle fossa

## GENERAL COMMENT

There are few reports on surgical treatment of chordomas, although with the increasing tendency for neurosurgeons to explore regions of the cranial cavity previously considered inaccessible an experience is being accumulated. In none of the cases of chordoma reviewed by Jelliffe and Larkin<sup>16</sup> in 1912 was the patient subjected to surgical exploration. Hass,<sup>2</sup> in 1934, found records of 25 instances in which surgical removal of the growth was attempted. He stated that of the patients who survived, few were benefited, the growth recurring in from six to eighteen months. However, it is notable that this is by no means the rule, and a completely pessimistic attitude toward these tumors is not warranted. Reference is made to the case reported by Klotz,<sup>17</sup> in which four and one-half years intervened before recurrence was evident. In several publications note is also taken of the second case recorded by Bailey and Bagdasar.<sup>10</sup> In this instance a biopsy specimen of the growth had been taken by Cushing through the transphenoid route. The patient lived five years after operation, roentgen therapy having been instituted after the procedure.

At operation the gross appearance of the well encapsulated tumor is not unlike that of an aneurysm. Frequently it is possible to separate with considerable ease the compressed and stretched cranial nerves from the outer aspect of the tumor. Occasionally, however, as in the case reported by Hass,<sup>2</sup> the cranial nerves are encircled with tumor tissue. Similar involvement of the basilar artery may be present, adding to the difficulty of complete removal. The area of attachment to the basilar bone is usually relatively small, measuring from 1.5 to 2 cm. in diameter. However, through this small area of attachment erosion and even perforation of the bone may take place, with nasopharyngeal extension. It is practically impossible to remove this adherent portion of the tumor.

Another tendency which adds to the difficulty of any attempt at extirpation is the manner in which the growths, arising in the posterior fossa, extend over the petrous ridge to spread widely in the middle fossa, usually adjacent to the sella. This is well illustrated in the first and third cases reported here and in the first case reported by Van Wagenen.<sup>8</sup> Occasionally erosion of bone may take place in the region of the extension, as in case 3.

In the absence of the characteristic notching of the basilar plate on roentgen examination, there is no means of making an absolute diagnosis prior to surgical exploration. However, multiple cranial nerve palsies, particularly when associated with evidence of a lesion in the middle

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16. Jelliffe, S. E., and Larkin, J. H.: Malignant Chordoma Involving the Brain and Spinal Cord, *J. Nerv. & Ment. Dis.* **39**:1-16, 1912.

17. Klotz, A.: Chordome malin du nasopharynx, *Semaine d. hôp. de Paris* **7**:56 (Jan. 31) 1931.

fossa, are highly suggestive. The diagnosis is even more likely when air studies indicate upward displacement of the third ventricle, the aqueduct of Sylvius and the fourth ventricle. This ventriculographic picture, characteristic of expansile lesions of the midline involving the basilar plate, is well illustrated in the article by Van Wagenen.<sup>8</sup> It should be noted, however, that other types of growths may involve the basilar bone. Upward and posterior displacement of the fourth ventricle by a midline tumor, apparently a meningioma, has been described by Turner and Lutz.<sup>18</sup> In this instance planigraphy was used to visualize the air-filled ventricular system. A complete discussion of meningiomas of the basilar groove was given by Cushing and Eisenhardt<sup>19</sup> in their recent monograph.

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18. Turner, O., and Lutz, W.: Planigraphic Studies of the Fourth Ventricle: Preliminary Report with an Illustrative Case, *Yale J. Biol. & Med.* **12**:251-253 (Jan.) 1940.

19. Cushing, H., and Eisenhardt, L.: *Meningiomas: Their Classification, Regional Behavior, Life History and Surgical End Results*, Springfield, Ill., Charles C. Thomas, Publisher, 1938, pp. 171-180.

## REVIEW OF UROLOGIC SURGERY

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### KIDNEY

*Tuberculosis.*—Wildbolz,<sup>1</sup> discussing the early diagnosis and treatment of renal tuberculosis, stated that in many cases in the very early stages of renal tuberculosis the only symptom of the disease is bacilluria. In other cases, however, in addition to bacilluria, slight albuminuria may be observed, together with slight leukocyturia. Many reports have given rise to the impression that in a tuberculous patient tuberculous bacilluria may be present without active disease of the kidney and also that bacilluria without renal tuberculosis may be rather common. However, a survey of the literature fails to disclose a single instance of such a type of bacilluria, according to more modern critical evidence. Nor has it been possible to date to produce tuberculous bacilluria in the absence of tuberculous disease of the kidney. It has not been shown either clinically or experimentally that tuberculous bacilluria can arise from a healthy or a nontuberculous kidney. Thus, a discharge of tubercle bacilli from a kidney may well be accepted as evidence of the existence of a tubercle bacillus-discharging lesion in the organ.

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1. Wildbolz, H.: Die Diagnose und Therapie der Frühfälle von Nierentuberkulose, Internat. Soc. Urol., Rep. (pt. 1) 7:267-320, 1939.

Tuberculous renal infection demonstrated by bacilluria produces at the onset different types of scattered lesions in the kidney. In the most common form the lesions are exclusively or predominantly situated in the medullary part of the infected kidney, particularly in the papillae or in the calices. These lesions, with formation of typical tubercles, evidence a tendency toward early caseation and involvement of the renal pelvis.

In a second, less common type, early tuberculous lesions predominate in the renal cortex and in spite of their formation of typical tubercles have an early tendency toward fibrous atrophy rather than toward caseation.

The reason papillary lesions have a greater tendency toward caseation and formation of abscess than do those in the cortical region may, perhaps, lie in the fact that tubercles in the papillary region lead much more frequently to retention of urine in adjacent tubules than do cortical tubercles. Urinary stasis and urine-soaked granulation tissue offer favorable conditions for the development and increased virulence of the bacilli and therefore rapidly bring about caseation and formation of abscess. Furthermore, by reason of the decreased circulation of blood in the papillary region as compared with that in the cortical substance, the papillary tissue offers less resistance to the invading bacilli.

There is a third early form of the infection, without formation of tubercles. Tubercle bacilli seem to enter the renal tissue and become attached without producing tubercles, but they apparently cause a non-tuberculous inflammatory tissue reaction. The relation between tissue allergy and the number and virulence of the tubercle bacilli permits, through allergic reaction of the tissues, rapid destruction of bacilli. As a result they produce only a nontuberculous inflammation.

Early diagnosis of renal tuberculosis entails various difficulties, according to the anatomic type of the disease present. Caseous papillary tuberculosis, in which the lesions spread, as a rule, rapidly into the renal pelvis, causes pyuria and bacilluria early, as well as disturbed renal function, so that diagnosis is possible at a time when only minute caseous foci exist in the papillary region. Hence, the condition in almost all kidneys removed in the early stage of the disease belongs to this anatomic type of renal tuberculosis.

Less marked symptoms are produced by caseous tuberculous lesions not yet in open contact with the renal pelvis and also by the fibrous type of renal tuberculosis in the first stage of the disease. Tuberculous bacilluria may for some time be the only clinical symptom and afford the only basis for diagnosis.

Bacilluria demonstrable by means of animal inoculation and culture seems to occur rather early after tuberculous infection of the kidney. Therefore, bacteriologic examination of the urine makes diagnosis possible in the earliest stage.



Typical renal pyuria and rapidly decreasing secretion of the disabled kidney indicate the probable presence of caseous renal tuberculosis.

Although unilateral renal tuberculosis at the onset may be diagnosed easily and with certainty by the demonstration of bacilli in the renal secretion, it is difficult to detect the onset of tuberculous infection of the other kidney. Demonstration of the bacilli in the secretion of one kidney proves that tuberculous involvement of that kidney exists, provided that the lower part of the urinary tract is free from tubercles, but there is no absolute proof of bilateral renal tuberculosis when the secretion of the opposite kidney contains tubercle bacilli. The possibility that bacilli spread from the bladder into the ureter of the opposite kidney never can be definitely excluded. But initial tuberculosis of the opposite kidney may be diagnosed with absolute certainty when the secretion of that kidney contains, in addition to bacilli, leukocytes in abnormal numbers.

Treatment of initial unilateral renal tuberculosis differs according to whether the form is caseous or fibrous. The combination of unilateral bacilluria and pyuria associated with decreased function of the diseased kidney, making early caseous renal tuberculosis probable, demands immediate nephrectomy. However, if unilateral tuberculous bacilluria without pyuria and without clinically demonstrable loss of function is present, nephrectomy should be discouraged in spite of unilateral involvement, under the assumption that the disease process present is merely fibrous renal tuberculosis. General nonsurgical treatment for tuberculosis should be administered. But during this period accurate urinary control of the patient for from four to six months is necessary. Early symptoms of caseation must be carefully watched for, so that the only curative treatment, surgical intervention, will not be delayed when it is actually needed.

In the presence of early bilateral renal tuberculosis, nephrectomy is indicated only when in the course of years the stage of the disease in the two kidneys differs to a great degree.

Thomas, Stebbins and Rigos<sup>2</sup> reported on the results of their studies and investigations of the methods of diagnosis and treatment of renal tuberculosis during their service as members of the staff at Glen Lake Sanatorium at Oak Terrace, Minn. This institution is owned by Hennepin County and contains 700 beds. Patients are admitted for the diagnosis and treatment of all types of tuberculosis.

The authors' historical data reveal that various lesions of tuberculosis, including those found in the kidney, were present in the human body five thousand years before Christ.

In 1825 Pierre C. A. Louis discovered that lesions of tuberculosis in the thorax always precede extrapulmonary lesions. This statement

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2. Thomas, G. J.; Stebbins, T. L., and Rigos, F. J.: *The Diagnosis and Treatment of Renal Tuberculosis*, Internat. Soc. Urol., Rep. (pt. 1) 7:321-370, 1939.

was universally accepted, even in 1825, by all physicians and surgeons interested in the diagnosis and treatment of all forms of tuberculosis, so that it was formulated into what is recognized today as "Louis' law."

After the first successful removal of a tuberculous kidney, in 1872, the operation became popular, and by 1892 renal tuberculosis was the leading indication for nephrectomy. When it became possible to find tubercle bacilli in the urine which came from one kidney, the only treatment prescribed was surgical removal of that kidney, provided that gross evidence of infection was not observed in the other kidney.

Pathologic examination and careful clinical observation demonstrate that any lesion of tuberculosis outside the thoracic cavity is evidence of hematogenous spread. Therefore, a renal lesion must be a local manifestation of a disease which is or can be general. It is evident today that tuberculosis of the kidney is secondary to tuberculosis situated elsewhere in the body, most often in the thoracic cavity.

The data obtained from the postoperative follow-up reports of many surgeons who have removed large numbers of kidneys containing lesions of tuberculosis revealed that only 60 per cent of the patients who underwent unilateral nephrectomy survived more than two years. After the infected kidney had been surgically removed, the patients still had active lesions of tuberculosis in some organs or tissues; many of these lesions were situated in the remaining kidney.

The pathologists' interest in the early lesions of renal tuberculosis was not aroused until Medlar, in 1925, published his epoch-making work. Medlar, a pathologist, examined the kidneys of many persons who had died from pulmonary tuberculosis. The first startling fact he discovered was that both kidneys obtained from every patient contained multiple lesions of tuberculosis. None of the patients from whom these kidneys had been removed had symptoms referable to the urinary tract or symptoms that would have suggested renal tuberculosis.

Data obtained from clinical research aimed at the discovery of early lesions of renal tuberculosis in patients who had other lesions of this disease, plus a certain amount of pathologic study, revealed that the authors' conclusions are the same as those promulgated by Medlar. In addition, it has been demonstrated satisfactorily that the kidney does resist the destructive effect of *Mycobacterium tuberculosis* and that certain small lesions may be temporarily or permanently arrested, just as similar lesions may be controlled or arrested in other organs or tissues of the human body. The authors' study of the diagnosis and treatment of the early lesions of tuberculosis of the kidney has convinced them that treatment other than surgical intervention may result in the arrest and possible cure of these lesions. Large, destroyed regions of tuberculosis in the kidneys of patients in private or clinical practice who are seeking relief from the typical symptoms of vesical tuberculosis (a secondary and late lesion of urogenital infection) may not be cured by medical

means alone. The authors have demonstrated, however, that in patients with destroyed regions of tuberculosis in both kidneys a general and local defense mechanism may develop which will protect the patient and the kidney from the continuous destructive effects of *Myco. tuberculosis*.

Urologists should be prominent and active members of the staff of every institution in which tuberculosis is being treated. If the urologist is given the opportunity, he will be able to make the diagnosis and to suggest treatment of early renal disease before the kidney is destroyed and before other urogenital organs are permanently incapacitated.

Thomas, Stebbins and Rigos<sup>2</sup> conclude that:

1. There is an early as well as a late stage of renal tuberculosis, just as there are such stages in any other type of tuberculous infection. In this stage the condition may be symptomless, but a careful search will reveal clinical observations sufficient to make a diagnosis possible.
2. A study of the early lesions of renal tuberculosis must be undertaken while the patient is under treatment in a sanatorium. It is during the active stage of the original pulmonary or extrapulmonary lesion of tuberculosis that the kidney becomes infected and the early lesions develop.
3. Any patient who has pulmonary or extrapulmonary lesions of tuberculosis may have unrecognized renal involvement. Repeated urinalyses, the injection of urinary sediment into animals and complete urologic studies should be carried out before a diagnosis which excludes renal tuberculosis is given.
4. The route of spread of the bacilli of tuberculosis from the thoracic cavity to the kidney is through the blood stream.
5. A normal kidney does not eliminate the bacilli of tuberculosis.
6. The local renal lesion produced by the bacilli of tuberculosis is not a local disease but a local manifestation of a general disease.
7. In the organs and tissues of the human body, resistance against *Myco. tuberculosis* may develop, which may be manifest in the kidney as well as elsewhere.
8. The progress of lesions caused by tuberculosis of the kidney, as well as the progress of tuberculous lesions situated elsewhere, is slow.
9. Tuberculosis of the kidney does not present a pathologic picture different from that of tuberculosis of other organs. When tuberculosis of other organs or tissues is studied, this fact becomes apparent.
10. Bilateral renal infection occurs in between 47 and 51 per cent of all patients who have tuberculosis of the urogenital structures (60 to 70 per cent during the invasive stage). Repeated examinations, including the making of bilateral pyeloureterograms, are necessary to prove the absence of nondestructive tuberculous lesions in an apparently sound kidney.

11. The primary focus of tuberculosis in the urogenital tract is most often the kidney. Early tuberculosis of the urogenital apparatus is usually symptomless.

12. Pyeloureterograms may show definite evidence of a pathologic lesion in a kidney when results of examination of the urine for the bacilli of tuberculosis from this kidney are negative.

13. Bilateral pyeloureterograms are major factors in the making of a positive diagnosis of renal tuberculosis in 27 per cent of instances. They are valuable in enabling the urologist to follow the progress of destructive lesions.

14. The finding of Myco. tuberculosis in catheterized ureteral urine from one kidney does not in itself constitute an indication for nephrectomy, even if results of examination of the urine from the other kidney are negative.

15. Treatment for every patient who has renal tuberculosis is both medical and surgical. How long the medical treatment should be continued before surgical treatment is started depends entirely on the condition present and the care with which the diagnosis has been made.

16. Clinical and pyelographic evidence indicates that a nondestructive lesion of renal tuberculosis will heal. A patient who has this type of lesion should have the advantage of treatment in a sanatorium to assist him in building up the necessary resistance against the destructive effect of Myco. tuberculosis.

17. Before he attempts removal of a kidney known to contain a lesion of tuberculosis, the urologic surgeon should be sure that the other kidney is sound and that other lesions of tuberculosis have been arrested. This may require months of observation and repeated inoculation of animals with urinary sediment.

18. Every patient who has submitted himself for surgical removal of a tuberculous kidney should receive medical treatment after the operation.

19. The prevalence of renal tuberculosis is decreasing.

20. The character of the lesions of renal tuberculosis is changing.

Colby<sup>3</sup> stated that patients who have renal tuberculosis are so benefited by treatment in a sanatorium before operation that this type of treatment should be a part of routine care. Operation is seldom advisable until the patient shows evidence of increased resistance to the disease. The type of service recommended is best rendered by institutions which are devoted to the care of extrapulmonary tuberculosis, and few communities have such hospitals. Renal and genital lesions complicate

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3. Colby, F. H.: Renal Tuberculosis and Sanatorium Care, *J. Urol.* **44**: 401-405 (Oct.) 1940.

tuberculosis of the bones more frequently than is generally supposed, and constant albuminuria is an early indication that the kidney may be involved.

*Anomaly.*—The most common type of horseshoe kidney is that in which fusion of the lower pole occurs by means of an isthmus which consists of renal tissue and which lies in front of the great vessels. Numerous variations of this type are found.

Meek and Wadsworth<sup>4</sup> reported a case in which the horseshoe kidney lay between the great vessels. The right kidney lay in a transverse position and extended across the vertebral column. The left kidney was situated entirely to the left of the midline, and its long axis was parallel to the vertebral column. Fusion between the two had occurred at the lower poles.

The vena cava passed over the right kidney, lying anterior to it and crossing it in its lateral half. The aorta lay behind the right kidney at about its middle. The line of fusion was situated 4.5 cm. to the left of the midpoint of the aorta. The portion of the mass crossing the midline lay over the lower half of the second and the upper half of the third lumbar vertebra.

The vascular system was much more extensively developed on the left side. All the vessels, however, seemed to have had their origin in a single segment. The renal arteries stemmed from the aorta at the same level. The right renal artery passed down beneath the vena cava and after giving off a branch to the right adrenal artery divided into three branches.

Numerous other anomalies were found. These included an anomalous situation of the carotid and subclavian arteries, an unusual position of the right recurrent laryngeal nerve, congenital fusion of two pairs of vertebrae, an extra rib on the right associated with fusion of two pairs of ribs on the left, an anomalous muscle of the left part of the thorax and many other minor developmental abnormalities.

Quinn<sup>5</sup> reported a case of bilateral renal ectopy. The patient was a Negro aged 31 who complained of pain in the lower part of the abdomen. On abdominal exploration a kidney-shaped mass was found low on the right side, behind the peritoneum. Later, roentgen examination demonstrated the presence of bilateral renal and ureteral opacities in the sacral region. Moderate hydronephrosis was present. Results of functional tests showed comparatively normal renal function.

Twenty-seven similar cases have been reported in the literature.

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4. Meek, J. R., and Wadsworth, G. H.: A Case of Horseshoe Kidney Lying Between the Great Vessels, *J. Urol.* **43**:448-451 (March) 1940.

5. Quinn, W. P.: A Case of Bilateral Renal Ectopy, *J. Urol.* **44**:10-12 (July) 1940.

to establish the diagnosis. The Casoni cutaneous reaction was positive for echinococcic disease, but the results of fixation of the complement were negative.

*Infections of Renal Cortex.*—Kahle, Green and Tomskey<sup>8</sup> reported 11 cases of staphylococcic infection of the renal cortex. The symptoms of cortical abscess seem to develop more rapidly and the febrile reaction seems to be consistently more marked than is the case in the presence of carbuncle. Pain in the loin was invariably present with both conditions, but rigidity of the lumbar muscles varied in degree and was sometimes absent. The leukocyte count was generally higher when carbuncle was present, and the percentage of polymorphonuclear leukocytes was lower in the presence of carbuncle than in the presence of cortical abscess. Culture of the blood was not helpful in the formation of a diagnosis. The urine, except in 1 case, in which the abscess had ruptured into the calix, was consistently normal. Culture of material from the kidney and of vesical urine usually showed no growth. Cystoscopic examination showed no changes in the mucosa of the bladder. Roentgen and pyelographic examination failed to supply information in about half the cases.

The diagnosis of cortical abscess or carbuncle usually can be made on the basis of history, physical observations and laboratory data, but differentiation between carbuncle and abscess usually cannot be made with certainty. Determination of previous furunculosis or of some similar condition is helpful. The presenting symptoms frequently are not proportionate to the degree of pathologic change found at operation.

Kahle, Green and Tomskey<sup>8</sup> concluded that, although carbuncle and abscess of the kidney frequently resemble each other clinically, they are not identical and differ materially in pathologic aspects. Therapy is essentially surgical, but radical operation is not always necessary. A lower mortality rate seems in general to follow nephrectomy, but excellent results can be achieved by conservative procedures in properly selected cases. Early diagnosis and prompt surgical intervention decrease the mortality rate and the postoperative morbidity rate, and the time element is therefore an important factor in the final outcome.

*Necrosis.*—A review of the 40 proved cases of symmetric cortical necrosis of the kidneys reported in the literature suggests that the renal condition is a pathologic manifestation of extremely severe toxemia of pregnancy. There are no characteristic symptoms which enable the urologist to predict the development of symmetric cortical necrosis. Premature delivery of a dead and usually macerated fetus, followed at once by anuria, is the rule. Progressive retention of nitrogen in the blood

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8. Kahle, P. J.; Green, M. M., and Tomskey, G.: Staphylococcal Infections of the Renal Cortex: An Analysis of Five Additional Cases of Carbuncle and Six Additional Cases of Abscess, *J. Urol.* **43**:774-792 (June) 1940.

common, but the clinical picture resembles more closely that associated with bilateral ureteral obstruction than that associated with classic uremia.

Although the condition is usually fatal, 1 case has been reported in which recovery followed decapsulation.<sup>9</sup> Microscopic proof of the diagnosis was obtained from a portion of the renal substance removed at the time of operation. This condition may not be uncommon, and for every patient who dies there may be a number of patients with less extensive involvement who recover without a diagnosis having been made.

Although there are no characteristic manifestations of any type of impending renal cortical necrosis, the toxemia can be anticipated and avoided. All patients who show any sudden increase in weight should have rest in bed, elimination of sodium salts, restriction of fluids to a normal intake and adequate catharsis.

Davis<sup>9</sup> reported a case in which the description of the kidneys as seen at necropsy was characteristic of the observations in this condition.

The kidneys were similar and of approximately normal size. The capsule peeled spontaneously from a smooth, remarkably pale light brown surface. On the cortex was a similar light gray brown, sharply demarcated from the gray medulla, which was of approximately normal color. . . . In the kidneys the striking cortical changes were infarcts due to occlusion of the small branches of the renal artery by organizing thrombi. The infarcted portion extended from the medulla to the capsule, with the frequent exception of a narrow subcapsular rim of living tissue nourished by capsular vessels. Tubular and glomerular architecture could be made out but all cellular detail was lost. Nuclear fragments were scattered through the bright red staining necrotic cytoplasm. The arteries were occluded by masses of old red staining fibrin, which was frequently almost completely replaced by young fibroblasts growing from the subendothelial tissue. Many of the collecting tubules were filled with plugs of albuminous material.

#### RENAL HYPERTENSION

Braasch, Walters and Hammer<sup>10</sup> made a study of readings of blood pressure in 975 consecutive cases collected from files at the Mayo Clinic to determine the incidence of hypertension in an average group of adult patients. To determine whether the incidence of hypertension is increased in the pathologic changes observed in the so-called surgical kidney, study was then made of the records of a group of 1,684 patients who underwent surgical operations on the kidneys at the clinic. Hypertension occurring in the presence of a unilateral lesion of the kidney was frequently relieved by operation on the kidney.

The incidence of hypertension in a group of 1,684 patients who underwent renal surgical operations was no higher than it was in a group of patients taken at random.

9. Davis, C. H.: Symmetrical Cortical Necrosis of Kidneys, *J. A. M. A.* 2370-2372 (June 15) 1940.

10. Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, *Proc. Staff Meet., Mayo Clin.* 15:477-478 (July 24) 1940.

Two cases of obstructive nephropathy with resultant hypertension were presented. Results of appropriate treatment in these cases clearly demonstrated that the causal relation between obstruction and hypertension is not renal insufficiency and suggested a reflex rather than a toxic or humoral origin, since nephrostomy was as effective as nephrectomy in restoration of the blood pressure to normal values.

In 1 case malignant hypertension occurred ten years after injury to the kidney. The possibility of a causal relation between ischemic changes in this kidney and the hypertension which was observed suggested the advisability of making periodic determinations of blood pressure in all cases after trauma to the kidney. The development of hypertension in such circumstances would appear to make prompt nephrectomy a rational procedure.

MacKenzie and Seng<sup>13</sup> stated that hypertension in patients who have pyelonephritis is relatively common. When pyelonephritis is unilateral and is in the advanced stage, removal of the kidney has in many cases reduced the pressure permanently.

Many of these kidneys are found in very young patients and are of the small contracted type. With such patients, certainly with those in the ischemic group, a congenital element may in a measure be responsible.

Until these questions can be answered more satisfactorily, surgical treatment in early stages of the condition must still be regarded as experimental. In the presence of polycystic kidneys, the advisability of surgical intervention for hypertension seemed questionable to MacKenzie and Seng<sup>13</sup> at the time of their writing.

In the presence of obstructive lesions, they wrote, the procedure is much clearer and relief of the obstruction is always indicated.

Koons and Ruch<sup>14</sup> reported a case in which hypertension afflicted a 7 year old girl who had a Wilms tumor. Nephrectomy relieved the condition.

The specimen removed at operation consisted of a tumor mass and kidney 15.5 by 10 by 9 cm. A small, firmly circumscribed portion, apparently of renal tissue, was seen, although on section the architectural markings were not apparent. On section the tumor itself was soft and yellowish gray, with small portions of hemorrhagic infiltration. A few cystlike cavities were filled with a yellowish gelatinous fluid. The pathologic diagnosis was embryoma of the kidney (Wilms tumor).

The exact mode of interference with renal circulation in this case was not apparent, but it was probably due to pressure of the tumor

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13. MacKenzie, D. W., and Seng, M. I.: Urological Aspects of Hypertension. *Surg., Gynec. & Obst.* **70**:578-583 (Feb. 15) 1940.

14. Koons, K. M., and Ruch, M. K.: Hypertension in a Seven Year Old Girl with Wilms' Tumor Relieved by Nephrectomy. *J. A. M. A.* **115**:1097-1099 (Sept. 28) 1940.



ue, which invaded the renal pedicle and the adjacent lymph nodes. The compactness of the tissues in that region was most evident at operation, before the kidney was freed from its bed. Another possibility is that the neoplastic mass, which almost entirely surrounded the kidney, acted in the same manner as the cellophane envelope used by us to produce experimental hypertension. Hypertension in this case could scarcely have been referable to some product of the tumor itself, because metastasis was found, yet the blood pressure returned to a normal value.

Barker and Walters<sup>15</sup> reported 5 cases of unilateral chronic atrophic pyelonephritis associated with hypertension in which the blood pressure returned to and persisted at normal levels after nephrectomy. None of these patients had advanced organic arterial damage; all had a relatively normal diastolic pressure as compared with the systolic pressure, and in 3 patients concerning whom the element of time was definite hypertension had not long existed. All patients had chronic unilateral atrophic pyelonephritis with contraction of the diseased kidney to less than half the normal weight and with marked arterial thickening in the scarred region. Since these regions comprised a large portion of the renal tissue in each case, there can be no doubt that there was considerable obstruction to the renal arterial flow. Because of the relation of these changes to hypertension and the excellent results obtained for these 5 patients, the authors reviewed a series of 57 consecutive cases of chronic atrophic pyelonephritis and found that in 45.6 per cent the systolic blood pressure was more than 145 mm. of mercury. Likewise, they studied 24 cases in which chronic atrophic pyelonephritis was disclosed at pathologic examination after nephrectomy and found in 62.5 per cent the blood pressure was elevated and that in 45.8 per cent definite hypertension was present.

All these studies led to the conclusion that, although localized renal neoplasms are uncommon in cases of essential hypertension, when there is thickening and contraction of the arterial walls, such as are seen in the presence of atrophic pyelonephritis, hypertension will result and will be relieved by removal of the diseased kidney.

Horton<sup>16</sup> made a statistical study of the relation of hypertension to renal neoplasm. He stated that the presence of hypernephroma and hypertension, with disappearance of hypertension after removal of the tumor, and recurrence of the hypertension associated with recurrence of the hypernephroma, certainly suggest a causal relation.

Barker, N. W., and Walters, W.: Hypertension and Chronic Atrophic Pyelonephritis, *J. A. M. A.* **115**:912-916 (Sept. 14) 1940.

Horton, B. T.: The Relationship of Hypertension to Renal Neoplasm, *Staff Meet., Mayo Clin.* **15**:472-474 (July 24) 1940.

He considered a total of 491 cases of all types. A systolic blood pressure of 140 mm. of mercury and a diastolic blood pressure of 90 mm. were regarded as the upper limits of normal. The renal tumors were divided arbitrarily into two groups: (1) hypernephromas and (2) tumors of other types, which included papillary squamous cell epitheliomas, sarcomas and hemangioendotheliomas.

A summary of the study follows: There were 335 cases of hypernephroma. Two hundred and forty-seven men and 88 women were affected. Approximately 60 per cent of the men had normal blood pressure, and approximately 40 per cent had hypertension. Of the 88 women who had hypernephroma, approximately 45 per cent had normal blood pressure, and approximately 55 per cent, hypertension. Taken as a group, 188 of the 335 patients who had hypernephroma had normal blood pressure; 144 had hypertension, and 3 had hypotension. Of the 144 who had hypertension, the blood pressure of only 46 was recorded after nephrectomy; of these 46, 18 had normal blood pressure and 28 had hypertension. One hundred and twenty-four patients had other renal tumors. Of these, 67 had normal blood pressure and 57 had hypertension. Of the 67 patients who had normal blood pressure, the pressures of 18 were read after operation. Of these 18, 12 had normal blood pressure, 4 had hypertension and 2 had hypotension. Of the 57 patients who had hypertension, records were obtained of 25 after nephrectomy, and of these, 11 had normal blood pressure and 14 still had hypertension.

No consistent alteration in blood pressure followed removal of a tumor of either type. This was particularly significant in cases of hypernephroma, in which about as high an incidence of hypertension occurred after removal of the tumor as had existed prior to the operation. There was no constant increase in the blood pressure of patients suffering from renal tumors, and this study failed to substantiate the observation of previous investigators that marked diminution of antecedent hypertension follows removal of a hypernephroma.

#### TUMORS

Kozoll and Kirshbaum<sup>17</sup> reported 33 instances of hypernephroid adenoma or benign hypernephroma, is all of which the tumors were observed incidentally post mortem. Six of these benign growths occurred simultaneously with another unrelated type of malignant tumor. The tumor was usually smaller than 5 cm. in its greatest diameter.

Kozoll and Kirshbaum also presented 44 cases of hypernephroid carcinoma or hypernephroma. In 6 of the 44 cases the carcinoma was

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17. Kozoll, D. D., and Kirshbaum, J. D.: Relationship of Benign and Malignant Hypernephroid Tumors of Kidney: Clinical and Pathological Study of Seventy-Seven Cases in 12,885 Necropsies, *J. Urol.* **44**:435-449 (Oct.) 1940.

an incidental postmortem observation; the malignant characteristics were obvious on gross examination. In 6 additional cases in which lesions appeared to be benign on gross inspection, they subsequently were proved to be malignant; invasion of the capsule and adjoining renal parenchyma had occurred, and tumor thrombi were present in the arcuate veins near the renal cortex. These changes were interpreted as the earliest evidences of malignant transformation. This experience led to the conclusion that a hypernephroma, regardless of size, can be considered benign only after metastasis and invasion have been excluded.

Kozoll and Kirshbaum<sup>17</sup> stated that hypernephroma is a tumor of varying histologic features with a developmental cycle of long standing. They wrote that the benign hypernephroid adenoma is potentially malignant and may be the precursor of hypernephroid carcinoma.

*Vascular Pedicle.*—Pick and Anson<sup>18</sup> studied the renal vascular pedicles of 200 cadavers. On the basis of their studies the following conclusions may be drawn:

Multiple renal veins are rare on the left side (they were found in only 2 of 200 cadavers, or 1 per cent), whereas they are common on the right (54 of 194 sides examined, or 27.8 per cent).

On the basis only of the number of vessels examined in the study of Pick and Anson<sup>18</sup> (and considering both sides), the renal pedicle in 39 per cent of the specimens (78 of 200) was composed bilaterally of two vessels.

Bilateral equality in the total number of vessels in the pedicles occurs in 49.5 per cent of cases (in the study alluded to, it occurred in 99 of 200 cadavers).

Single renal arteries and veins on both sides in the same specimen occur in 38.5 per cent of cases (they occurred in 77 of 200 cadavers), whereas a single renal artery and vein compose the pedicle in 59.5 per cent of sides (in 239 of 400 sides of cadavers examined).

It is commonly stated that the right renal artery is longer than the left renal artery and that the left renal vein is longer than the right. Although this is anatomically true, actually the length of the two pedicles from a surgical standpoint (permitting free mobilization) is about the same; on the right side the lateral border of the vena cava offers a fixed point for the renal arteries, whereas on the left the lateral border of the aorta functions in a similar manner. From the urologic standpoint, difference in the length of the pedicles is more apparent than real.

Although it is true that ligation of the large collateral vessels of the dorsum of the left renal vein, just lateral to the aorta, would free the

18. Pick, J. W., and Anson, B. J.: The Renal Vascular Pedicle: An Anatomical Study of Four Hundred and Thirty Body-Halves, *J. Urol.* **44**:411-434 (Oct.) 1940.

vein more completely, the left renal arteries are short; therefore, such a procedure would be of little surgical benefit. On the right it would be necessary to liberate the renal arteries from the dorsum of the vena cava—a dangerous method of mobilization. Even if such a procedure were successful, the right renal veins, being short, would nullify the effect of securing greater freedom for the right renal arteries.

Additional renal veins, which occur less frequently than supernumerary arteries, often communicate on the left side with other visceral veins (adrenal and spermatic or ovarian veins), with a retroaortic venous plexus and with the left lumbar and hemiazygos veins. Not infrequently the regular vein passes in front of the aorta and the supernumerary vein passes behind the aorta, forming (between the left kidney and the vena cava) a circumaortic venous ring.

Of surgical interest are those cases in which the gonadal vessel merely crosses the renal pedicle and those in which the vessel follows the renal artery in a transverse course before it descends on the left side, hooking around the suprarenal tributary of the renal vein. Spermatic or ovarian arteries may arise directly from the renal artery, thus being, proximally, constituents of the renal pedicle.

Mussey and Lovelady<sup>19</sup> studied pyelitis in its possible relation to the preeclamptic toxemia of pregnancy. They stated that from 1924 to 1937 inclusive there were 5,960 deliveries at the Mayo Clinic, with an incidence of pyelitis of 2 per cent. Of 117 patients who had pyelitis of pregnancy, 3 were afflicted by acute hypertensive toxemia and a fourth was afflicted fatally by an inflammatory renal lesion. Of 163 patients who had preeclamptic toxemia or eclampsia, 6 exhibited symptoms of pyelitis in the puerperium; none gave a history of pyelitis prior to the first pregnancy. When treatment was instituted early, a large majority of the patients who had pyelitis responded with reasonable promptness to the usual medical methods of treatment, so that in recent years (that is, in this particular clinic) the necessity for urologic consultation has been infrequent.

Mussey and Lovelady<sup>19</sup> stated that women suffering from undoubted renal disease should be advised against subsequent pregnancy. Some patients recover from acute renal disease, and in others the residual damage is so mild as to escape detection by the usual methods of examination. Among the patients who had pyelitis, 30 had one or more subsequent pregnancies; in 2 cases of the 4 previously mentioned (3 of acute hypertensive toxemia; 1 of an inflammatory renal lesion, in which death occurred) toxemia developed during a subsequent pregnancy.

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19. Mussey, R. D., and Lovelady, S. B.: Is There a Clinical Relationship Between Pyelitis of Pregnancy and Pre-Eclamptic Toxemia? *Am. J. Obst. & Gynec.* **39**:236-242 (Feb.) 1940.

Results in the cases reported would indicate that acute pyelitis of pregnancy when treated promptly is not in itself especially likely to cause preeclamptic toxemia or eclampsia and that after one attack of acute pyelitis of pregnancy the majority of women do not exhibit symptoms of residual renal damage.

*Calcification.*—Anderson<sup>20</sup> observed microscopic deposits of calcium in routine sections obtained from 180 (12 per cent) of a series of 1,500 patients who came to necropsy. In the group were cadavers of 540 infants or children, among which 31 (5.7 per cent) with renal calcification were observed. Among the cadavers of 960 adults, 149 (15.5 per cent) exhibited evidence of renal calcium deposition. Although the incidence of this condition among the cadavers of infants and children was less, calcification was more severe and massive in cadavers of infants and children than in cadavers of adults. In most cadavers of adults the deposits of calcium were small; frequently only a single mass of calcium was noted. There was invariably evidence of renal damage, and most of the calcification appeared to be of the dystrophic type. The cortex was more commonly involved than was the medulla. Early formation of calculus on the basis of deposition of calcium beneath the pelvic epithelium was noted in 2 instances. Massive calcification, such as occurs in association with hyperparathyroidism, was not observed. In no case was calcification severe enough to have exerted a significant effect on renal function during life.

#### URETER

*Transplantations.*—Hinman,<sup>21</sup> discussing ureterointestinal implantation and cystectomy for cancer, stated that the component subjects of his particular inquiry are vesical malignant tumor, ureterointestinal implantation and cystectomy. The plan of discussion was: part 1, published studies (a) of ureteroenterostomy and (b) of cystectomy, and part 2, personal studies, (a) experimental and (b) clinical.

In section *a* of part 1 (published studies of ureteroenterostomy) Hinman<sup>21</sup> said that the four main principles on which technic depends are the muscularizing principle, the intact orifice, the submucosal principle (valvular action) and the intact ureter. Published results (achieved by all methods except that based on the principle of the intact ureter) in 786 cases show: Five hundred and thirty operations were performed for benign conditions, with 159 deaths (30 per cent mortality rate); 212 operations were performed for malignant conditions, with 111 deaths (50

20 Anderson, W. A. D. Renal Calcification in Adults, *J. Urol* **44**:29-34 (July) 1940.

21 Hinman, F. The Technic and Late Results of Uretero-Intestinal Implantation, and Cystectomy for Cancer of the Bladder, *Internat. Soc. Urol., Rep.* (pt 1) **7**:464-555, 1939

per cent mortality rate); and 44 operations were performed for conditions not stated, with 24 deaths (54 per cent mortality rate). The totals are thus 786 operations for all conditions, 294 deaths and a mortality rate of 37 per cent.

In section *b* of part 1 (published studies of cystectomy for vesical cancer) Hinman<sup>21</sup> wrote that cystectomy was done 133 times after ureteroenterostomy (62 one stage operations and 37 operative deaths; 71 two stage operations and 14 operative deaths; 6 patients known to have survived for five years or more). Cystectomy also was done 117 times after other methods of ureteral disposal had been tried (8 patients known to have survived for five years or more). For an operable patient the risk of cystectomy, apart from the risk implied by diversion of urine, is less than 5 per cent, Hinman<sup>21</sup> wrote.

In section *a* of part 2 (personal experimental studies), Hinman<sup>21</sup> said that peritonitis is caused by leakage after operation, not by contamination at the time of operation. (It occurred 25 times in the course of ureteroenterostomy performed 172 times on 134 dogs.) Leakage follows faulty closure, failure of sutures to hold or unusual necrosis of the ureter or of the bowel. Oblique submucosal implantation is the best safeguard when it is performed with these precautions and precepts in mind:

1. The intestinal submucosa will hold sutures securely. Sutures placed in the serosa or muscularis easily slough through or tear out.

2. The adventitia is the only layer of the ureter for suturing.

3. A suture which penetrates the wall of the intestine or ureter is a potential cause of fistula.

4. Undue trauma of those parts of the intestine and ureter which are anastomosed will lower the patient's resistance to infection and may lead to gangrene. Leakage may follow necrosis. The ureter should be handled gently; it never should be pinched or pulled.

5. Injury to blood vessels, particularly to the submucosal vessels of the intestines and to some periureteral vessels, is dangerous. The ureter cannot always be stripped bare to the adventitia without the risk of such injury. It should be brought as cleanly as possible from its extraperitoneal bed and then left without further stripping. When all these conditions have been successfully fulfilled there need be no fear of peritonitis, the only reason for extraperitoneal implantation.

6. Contamination of the field will not cause peritonitis if the implantation is made and if the ureter remains secure. Nevertheless, contamination is bad; local infection or even abscesses may follow it.

Hinman<sup>21</sup> said that all the foregoing precautions and precepts apply to the prevention of ureteral obstruction. Early ureteral block resulting

from surgical edema, infectious tumefaction and massive gangrene of the end in excess are thought to be avoided by use of the principle of the intact ureter, previously mentioned. Yet 9 of 11 ureters so implanted (in 8 dogs) were found to be dilated, and the kidneys were found to be hydronephrotic, from thirteen days to seven months later.

In section *b* of part 2 (personal clinical studies), Hinman<sup>21</sup> wrote that the patient on whom cystectomy is to be done should be selected on a rigid basis, not alone on that of the seeming hopelessness of his condition without cystectomy but on that of operability. After uretero-enterostomy, cystectomy carries its own risk, to be reckoned with also under operability, a risk which is lowered when cystectomy is done at a second stage and when it is performed by a technic which produces perineal drainage in men and vaginal drainage in women.

With 9 patients, Hinman<sup>21</sup> reported, removal of all the cancer was found to be impossible. Of 16 remaining supposedly operable patients, 6 died, and their deaths were considered to be "surgical." The cause of death for 2 of these patients was pulmonary; the cause of death for 4 patients was faulty implantation technic. Of the 10 patients who survived surgical treatment, 1 lived almost five years and died of chronic pyonephrosis; 3 died of recurrence after one, one and a half and two years, respectively. Six were living and well at the time Hinman<sup>21</sup> wrote.

Gouverneur<sup>22</sup> discussed the technic and results of ureteral transplanation. The most important problem of ureteral implanation is competent establishment of the flow of urine after separation of the ureter from its normal orifice in the bladder. Uterocystoneostomy is implantation of the juxtavesical part of the ureter into the bladder. Little by little this operation, in spite of critics, has gained the approval of most surgeons, and study of remote results and functional tests has proved the value of this type of intervention; its success depends completely on the strictness with which the indications are formulated and on the perfection of the operative technic.

The procedure can concern only, in fact, the juxtavesical part of the ureter, or, more exactly, the last 5 cm. Its purpose is to reproduce as nearly as possible the normal conditions of ureteral function. The ureter must not have any kink in its course; it is necessary to avoid causation of any adhesion, any band or any possibility of occurrence of cicatricial stenosis; thus an attempt must be made to create a stoma sufficiently wide and supple. Any mechanical obstacle inevitably produces dilation of the urinary tree above the site of such an obstacle. It is necessary, therefore, to avoid all obstacles to the ureteral tract. Infection of the urinary excretory ducts is the great hazard of this particular type of

22. Gouverneur, R.: *Technique et résultats éloignés des transplantations de l'urètre*. Internat Soc Urol., Rep. (pt. 1) 7:373-451, 1939

reconstructive operation. Results will be essentially different according to the condition of the urinary tract and the walls of the ureter, particularly in the presence of ureteral infection and sclerosis with or without periureteritis.

In the performance of ureterocystoneostomy, the extraperitoneal approach is used by only a few surgeons; the transvesical approach is used for tumors of the bladder which make a large cystectomy necessary, and the transperitoneal approach is ordinarily used. In addition to these advantages, ureterocystoneostomy has the advantage that when it is employed, median laparotomy, usually already made, can be utilized, especially when a gynecologic operation is to be undertaken for a condition which is aggravated by a portion of a ureter.

Of the suturing procedures used, two seem to be the best. Richard's procedure is characterized by turning up the ureteral mucosa like the sleeve of a coat. Payne's procedure is simpler; it splits the ureteral end into two equal halves, which are fixed to the wall of the bladder. Gouverneur's<sup>22</sup> procedure is derived from the Payne-Marion technic; it has an advantage in that it permits the making of an oblique incision in the wall of the bladder, renders it unnecessary to place any suture in the ureteral mucosa, does not constrict the new orifice and does not require placing of an indwelling catheter in the ureter if no complications are present.

In the matter of indications for general surgical procedures, two different factors are to be considered. First, if recent section of the ureter has occurred, such as sometimes happens during total or simple hysterectomy or panhysterectomy, ureterocystoneostomy is the ideal method of reimplantation of the ureter in the bladder. Second, if ureteral fistula is the condition to be attacked, the decision is governed by the possible presence of infection of the urinary tract and the functional value of the kidneys.

In urologic surgical procedures, two different factors likewise must be recognized. First, if a congenital malformation or a ureteral stricture is present, reimplantation always should be done, and nephrectomy is necessary only in case of failure. Second, if cystectomy is to be done for cancer of the bladder, the selection of a procedure is dominated by the condition of the patient and the degree of progress of the cancer. If the tumor is small and the patient is strong, it is proper to try reimplantation; if the patient is too weak, it is better to do a rapid nephrectomy, because the immediate operative prognosis of reimplantation is more serious than that of rapid nephrectomy.

Gouverneur<sup>22</sup> has collected 156 cases and has retained only those in which a satisfactory postoperative functional examination was recorded; that is, examination by use of the cystoscope, examination by ureteral catheterization and ureteropyelographic examination. He found that



good late results were obtained in 40 per cent of 30 cases in which reimplantation was done for ureterovaginal fistula and in 60 per cent of cases in which immediate repair of sections of the ureter was done. Bad results are still numerous; infection of the urinary tract is one of the main reasons for this, as is stricture of the orifice. Every suture in an infected region is in fact a producing agent of sclerosis.

In discussion of ureterointestinal implantation it is necessary to study successively (1) the physiologic aspects of the ureter and of the ureterovesical segment, (2) the pathologic physiology of the new intestinal anastomosis of the ureter and (3) the results of operations, prognosis and surgical indications.

As to the first consideration (physiologic aspects of the ureter and of the ureterovesical segment), it should be remembered that urinary excretion depends on the integrity of two functions: contractions of the ureter and protection of the ureter against vesical backflow. Ureteral contraction can be produced in a normal way only if the vessels and nerves of the urinary tract are unimpaired; these vessels and nerves originate from various levels and are contained in the periureteral sheath. Any stripping of the ureter will disturb the nutrition of the ureter and, above all, disturbs its innervation. Protection of the ureter against vesical backflow is assured essentially by contraction of muscular fibers of the bladder itself, which surround the orifices of the ureter.

As to the second consideration mentioned (pathologic physiology of the ureterointestinal anastomosis), functioning of the anastomosis depends on two factors: (1) functioning of the cut and transplanted ureter on one side and (2) protection of this ureter against intestinal contraction on the other side. Cutting of the ureter and mobilization of it may disturb ureteral function, which has been well studied by Gouverneur;<sup>22</sup> it happens, in fact, that modifications of ureteral peristalsis at the level of the traumatized point may create a true dynamic obstacle. Protection of the ureter against intestinal backflow has been investigated by means of various technical procedures, which Gouverneur<sup>22</sup> classified into three groups according to their physiologic purposes: (1) direct ureterointestinal anastomosis, (2) anastomosis with muscularization of the ureter and (3) anastomosis with valves, whether done with the ureterovesical normal (conserved) valve or with valves formed by an artificial technical procedure.

In Gouverneur's<sup>22</sup> opinion, direct ureterointestinal anastomosis achieved by suture or by mechanical means is doomed to failure, because after such a procedure the ureter becomes an intestinal diverticulum and may have regurgitation into it with every increase of pressure; ascending infection is likely to be fatal.

In anastomosis with muscularization of the ureter by a technic derived from Witzel's procedure, a muscular duct is formed by suture of the intestinal wall above the ureter. Gouverneur<sup>22</sup> wrote that this procedure functions not by valvular action but by muscular constriction. At the moment of intestinal contraction the ureter is compressed in its juxta-intestinal tract, and intestinal backflow is thereby prevented.

Anastomosis with the ureteral valve is widely employed. Certain surgeons have retained the normal ureteral valve and have reimplanted it into the intestine.

Gouverneur<sup>22</sup> expressed the belief that the best known operation for creation of a mucous valve is Coffey's procedure, which has undergone innumerable modifications. According to Coffey, Gouverneur<sup>22</sup> said, the valve after the operation would act automatically. But study of operative procedures, Gouverneur<sup>22</sup> contended, proves that what occurs after Coffey's operation actually is muscularization of the ureter, which is grasped in a muscular buttonhole.

To be able to report on his third major consideration (results, prognosis and surgical indications), Gouverneur<sup>22</sup> studied remote results of implantation in the treatment of vesical exstrophy, complete epispadias, vesicovaginal fistula and ureterovaginal fistula and also the results of ureteral implantation in the preparation of patients for total cystectomy made necessary by vesical and ureterovesical cancers, either primary or metastatic.

Published cases of vesical exstrophy are not numerous; in 66 cases in which remote results were known, 75 per cent of the patients were followed for more than five years, and half were followed for more than ten years. Successful results of twenty and even thirty years' duration were recorded. Persons who have been operated on have been able to marry, and women have been able to undergo one or several pregnancies with normal delivery.

In the case of vesicovaginal fistula results are not numerous, because treatment of this condition by ureteral implantation is used only when the condition is very severe, with extensive vesicoureteral destruction. Of 24 patients who were followed, 10 obtained successful results which endured for more than three years.

In the case of vesical and ureterovesical cancer, ureteral implantation has permitted total cystectomy. Of 33 patients who were followed, 12 obtained successful results which lasted for more than two years. Death usually was caused by metastasis or local recurrence.

Surgical technic in ureteral implantation is of great importance, and it is necessary to have recourse to a procedure which is accompanied by a low immediate mortality rate. Coffey's technic, according to Gouverneur,<sup>22</sup> is by far the least severe of procedures. It was accompanied

by a mortality rate of 4 per cent in a series of 25 cases, and in a second series of cases there were no deaths. The procedures called "no. 1" and "no. 2," according to Gouverneur<sup>22</sup> are the best. The urologic surgeon, Gouverneur<sup>22</sup> concluded, must not forget the extreme importance of preoperative and postoperative care. He added that the difficulty of such operations as he mentioned requires much experience on the part of the surgeon.

After successful ureterointestinal implantation, urinary continence generally should be perfect. If some slight quantity of urine happens to remain in the colon after this operation, it will not initiate either local lesions or general disturbances.

Van Cappellen,<sup>23</sup> in discussing the technic of, and end results achieved by, transplantation of ureters, stated that urologists today are much farther advanced in knowledge of this field than in the days when Maydl first performed the ureteral operation that bears his name; on the other hand, urologists in general may not be satisfied with the results that have been obtained from ureteral transplantation to the time of writing (1939). The operative mortality rate accompanying this procedure is high (20 to 50 per cent), and the end results are not satisfactory. Besides, in many cases infection or obstruction (often combined) spoils the attempt to get good results.

After careful study of the literature and of his own 8 cases, Van Cappellen<sup>23</sup> discussed a method (the Van der Ven operation) which, to his knowledge, has not been used before except by Van der Ven in experiments and by Van Cappellen<sup>23</sup> himself in a clinical case. Van der Ven discovered that in using the Witzel principle for embedding the ureter in the wall of the bowel and by adding to it his own method of treating the stump of the ureter he obtained remarkably good results in dogs. He pointed out that most investigators know how easily a dog may become susceptible to infection and how much more difficult the operation is because of the smallness of the canine ureter. In the human being the operation can be done with more ease and security than in the dog.

Van der Ven turned the end of the stump of the ureter inside out and anchored this end in the bowel, taking care that the edges of the opening in the bowel and those of the stump came into close contact. After some weeks the result was an ideal opening of the ureter, which opening was elevated as a papilla above the mucosa of the bowel. This is in sharp contrast to the condition of the mouths of ureters when ureters have been transplanted in other ways; they then appear as more or less deep dimples in the mucosa. Necrosis and compression of the stump

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23. Van Cappellen, D.: *Technic and End-Results of the Transplantation of Ureters*, *Internat. Soc. Urol., Rep.* (pt. 1) 7:452-463, 1939.

did not develop after Van der Ven's operation, and dilatation and infection of the ureter and kidney, complications so greatly feared after ordinary methods of transplantation, did not occur.

Morson and Graham<sup>24</sup> stated that transplantation of ureters into the large bowel has become in recent years a recognized and justifiable surgical procedure. The most striking feature concerning immediate results in the series of cases reported by Morson and Graham<sup>24</sup> is the fact that no deaths occurred among patients not suffering from malignant processes, whereas the mortality rate for patients suffering from cancer was extremely high. The most careful preoperative preparation is essential if urinary infection is to be avoided. It is the practice to give a colonic "washout" each day for ten days; on the first and sixth of the days during this period an aperient agent is prescribed, so that the whole of the large bowel may be emptied. As a prophylactic measure against pyelonephritis, sulfanilamide in doses of  $7\frac{1}{2}$  grains (approximately 0.47 Gm.) is administered three times daily for four days immediately prior to the operation.

General anesthesia was employed in all cases in the series reported by Morson and Graham.<sup>24</sup> With the patient in the extreme Trendelenburg position, the abdomen was opened, and the incision was made from the umbilicus to the pubes; the pouch of Douglas (in the female) or the rectovesical pouch (in the male) was cleared of small intestine and transverse colon. An incision was made in the peritoneum along the line of the ureter from a point below the sacroiliac joint to the base of the bladder. The ureter was easily recognized by the presence of small vessels lying on its surface. The pelvic portion of the duct was then freed from the bed of cellular tissue in which it lay to the point at which it entered the wall of the bladder. Before the ureter was divided as it entered the wall of the bladder, a special clamp was placed an inch or two (2.5 to 5 cm.) above the point of division to prevent soiling of the peritoneum by urine. A Souttar needle was then passed through the proximal end of the ureter, and a portion of the ureteral wall was tied with catgut. Ligation of the distal stump followed, together with sewing of the peritoneum over the bed of the duct. The authors stated that insertion of the ureter into the pelvic part of the colon must be carried out with meticulous care, for it is in this part of the operation that an error in technic may produce fatal complications. That part of the pelvic portion of the colon which is chosen for the site of transplantation should be as near the promontory of the sacrum as possible;

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24. Morson, C., and Graham, W. H.: Transplantation of the Ureters into the Large Bowel and Its Effect upon the Kidneys, *Brit. J. Surg.* **27**:540-552 (Jan.) 1940.

it should be, roughly, where the bowel would lie with the patient in the erect position; thus the danger of kinking of the ureter will not arise and a minimum of tension will exist.

The technic of transplantation employed was that recommended by Wade, with certain slight differences, which were that the Mayo stitch was not used and that on the left side the ureter was not passed through a hole in the mesentary before it was inserted into the colon. A catheter was not inserted into the ureter. An incision about 2 inches (5 cm.) long was made in the peritoneal coat of the bowel, and the peritoneum on either side of it was separated from the muscle layer. It was necessary to maintain the colon in stretch while this was being done. A stab incision was made in the muscular coat and mucous membrane at the distal end of the 2 inch (5 cm.) incision, and through this the ureter, together with a Souttar needle, was passed into the lumen of the bowel. About an inch (2.5 cm.) of the duct was pulled into the bowel before it was fixed with the aid of the Souttar needle; this was considered important. The needle was brought out through all the coats, and the catgut suture was then tied. The surgeon then proceeded to bury the ureter beneath the peritoneal coat of the large intestine. He applied two lines of sutures to insure that there should be neither leakage of urine nor alteration in the desired position of the ureter. He transplanted both ureters at the same operation. It was also the custom to drain the pouch of Douglas (or the rectovesical pouch, as the case might be) for two or three days by means of a small rubber tube. The abdominal wound was closed in the usual way. Before the patient was returned to bed a tube was passed about 3 inches (about 7.5 cm.) into the rectum and was fixed to the thigh.

Little reaction or shock was encountered in any of the cases of Morson and Graham.<sup>24</sup> As a rule urine did not drain from the rectal tube until about thirty-six hours after operation; this, they wrote, is due to mechanical obstruction at the site of anastomosis. At the end of thirty-six hours urine was excreted rapidly and in increasing volume. After the first five days convalescence was apyrexial. Several patients on removal of the rectal tube immediately had complete control. In the others it developed in from twenty-four to forty-eight hours. Since 1936, 13 patients have undergone transplantation of ureters into the pelvic portion of the colon. Of these, 5 died, 4 of whom had malignant disease of the bladder and 1 of whom had secondary invasion of the trigon, the primary lesion being in the cervix. Thus, it will be noted, as has been stated, that it was only patients who had cancer who succumbed to the effects of the operation. The most striking case of all the series of Morson and Graham<sup>24</sup> was one in which a woman had complete procidentia, carcinomatous ulcers of the vagina and a bladder

full of stones. The malignant ulcers of the vagina had caused numerous hemorrhages, and it was the opinion of Morson and Graham that death would have been inevitable had not the patient undergone ureteral transplantation.

*Stone.*—Mayers<sup>25</sup> reported a case in which a giant ureteral calculus weighed 286 Gm. and measured 11 by 5.5 by 5 cm. This is the largest ureteral calculus reported in the literature. In Mayers' case anomalies of the urinary tract were present. They consisted chiefly of complete duplication of the right kidney and ureter and dilatation of all three ureters. There was also an anomaly of the sacrum and coccyx. Surgical intervention also was necessary for a calculus in the ureter on the opposite side; this calculus had descended from the kidney after surgical treatment for the giant calculus.

*Ureterostomy.*—Keyes<sup>26</sup> reported 6 cases in which cutaneous ureterostomy was done for tuberculosis. The operations of nephrectomy and contralateral ureterostomy were once performed simultaneously; ureterostomy preceded nephrectomy once and followed it 4 times. There were no postoperative deaths. There were, at the time of writing, no indications of the presence of tuberculosis in the kidneys or ureters of 3 patients since ureterostomy. Except for 1 patient, who needed meatotomy, these patients had had no treatment during a postoperative interval of three to nineteen years at the time Keyes<sup>26</sup> reported. Two of them were maintaining themselves dry by night as well as by day. One had married since ureterostomy, and another had given birth to a child. Three patients, who had tuberculosis in the surviving kidney, had to wear an indwelling ureteral catheter. Two patients who were followed had phosphatic stone within three years of ureterostomy. The progress of tuberculosis of the kidney was slow, Keyes<sup>26</sup> wrote, and other tuberculous lesions improved or healed. One patient had been alive thirteen years after ureterostomy at the time Keyes reported.

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(To Be Concluded)

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## FLUID REPLACEMENT IN SURGICAL STATES

WITH PARTICULAR REFERENCE TO TRANSFUSION OF ASCITIC FLUID:  
A CLINICAL AND EXPERIMENTAL STUDY

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AND

HARRY A. DAVIS, M.D.

NEW ORLEANS

The problem of fluid replacement has presented itself both to biologists and to surgeons. In man the loss of water, electrolytes or blood leads to disturbances which are progressive and which alter the normal response to replacement therapy. It is our purpose to present in this paper: (1) a study of the abnormal physiologic picture which results from loss of water, electrolytes and blood; (2) the technic of fluid replacement; (3) a critical evaluation of blood replacement fluids, and (4) the present status of transfusion of ascitic fluid.

The indications for fluid replacement fall into four main groups:

1. Loss of body water.
2. Loss of electrolytes.
3. Loss of whole blood.
4. Loss of plasma.

While it is convenient for purposes of discussion to separate each type of depletion state, in actual practice the distinction is not clearcut, and one will find frequently the merging of one state into another.

### LOSS OF BODY WATER

Loss of water from the body in excess of the intake of water results in dehydration. Similarly, desiccation of the blood is known as anhydremia. From the surgical point of view the causes of dehydration may be divided into two groups: (1) exogenous and (2) endogenous. Among the more important exogenous causes are voluntary or enforced deprivation of water, excessive sweating due to sunstroke, heat prostration, traumatic shock and surgical operations. Endogenous causes are prolonged diarrhea due to surgical lesions of the intestinal tract; vomiting

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due to obstructing lesions of the gastrointestinal tract, and inability to swallow liquids due to obstructing lesions of the esophagus.

The physiologic effects of dehydration may be considered at this point. Almost 68 per cent of the total loss of water comes from the muscles (Engels<sup>1</sup>), and the major portion of the remainder from the blood and skin (Durig;<sup>2</sup> Straub;<sup>3</sup> Tobler<sup>4</sup>). The composition of the blood is altered in the presence of dehydration. The specific gravity increases (Rominger<sup>5</sup>), and there is an increased concentration of red blood cells (Czerny<sup>6</sup>) and of hemoglobin (Underhill and Kapsinow<sup>7</sup>). As most of the loss of water from the blood is from the plasma, the concentration of plasma proteins is relatively greater than that of erythrocytes (Keith<sup>8</sup>). Thus plasma protein concentrations 50 to 100 per cent above normal have been reported (Reiss;<sup>9</sup> Marriott;<sup>10</sup> Berend and Tezner<sup>11</sup>). The rate of loss of water is important in determining the degree of hemoconcentration. When water is lost relatively slowly, hemoconcentration is not quite so great (Adolph<sup>12</sup>). When severe dehydration has lasted for some time, destruction of serum proteins, hemoglobin and red blood cells takes place, with a further loss of metabolic water (Lust;<sup>13</sup> Gürber;<sup>14</sup> Utheim<sup>15</sup>). It is evident that an examination of the blood during this stage will give a false impression

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7. Underhill, F. P., and Kapsinow, R.: The Influence of Water Introduction upon Blood Concentration Induced by Water Deprivation, *J. Biol. Chem.* **54**:459-464, 1922.

8. Keith, N. M.: Blood Volume Changes Following Water Abstinence, *Am. J. Physiol.* **59**:452-453, 1922.

9. Reiss, E.: Untersuchungen der Blutkonzentration des Säuglings, *Jahrb. f. Kinderh.* **70**:311-362, 1909.

10. Marriott, W. McK.: Anhydremia, *Physiol. Rev.* **3**:275-294, 1923.

11. Berend, N., and Tezner, E.: Die Wasserentziehung im Säuglingsorganismus bei akuten Gewichtsschwankungen, *Monatschr. f. Kinderh.* **10**:212-238, 1911.

12. Adolph, E. F.: The Regulation of the Water Content of the Human Organism, *J. Physiol.* **55**:114-132, 1921.

13. Lust, F.: Ueber den Wassergehalt des Blutes und sein Verhalten bei den ernährungsstörungen der Säuglinge, *Jahrb. f. Kinderh.* **73**:85; 179, 1911.



of the degree of dehydration. While the concentration of sodium chloride in the plasma is usually normal (Salge<sup>16</sup>), it may be increased when the dehydration occurs rapidly (Keith<sup>17</sup>). The level of blood phosphate rises as renal function diminishes (Howland and Marriott<sup>18</sup>). An increase in the concentration of nonprotein nitrogen and urea nitrogen occurs as a result of increased destruction of protein and failing renal function (Schloss and Stetson<sup>19</sup>). The level of blood sugar is raised (Marriott<sup>10</sup>), as is that of lactic acid in the blood (Clausen<sup>20</sup>). Definite acidosis is present, as evidenced by the increased hydrogen ion concentration of the venous blood (Sellards and Shakklee<sup>21</sup>).

The blood volume diminishes by as much as 40 to 50 per cent of the initial level, the decrease being mainly in the amount of plasma (Keith;<sup>8</sup> Rogers<sup>22</sup>). As the blood volume diminishes, a compensatory vasoconstriction occurs, leading to a diminished volume flow of blood, particularly in the extremities (Marriott;<sup>10</sup> Utheim<sup>15</sup>). The heart gives evidence of a diminished flow of blood through the coronary arteries, as indicated by the electrocardiogram (McCulloch<sup>23</sup>). The blood pressure, however, is usually not greatly lowered, provided that dehydration and anhydremia are gradual in onset (Feilchenfeld<sup>24</sup>). When anhydremia is produced rapidly in the experimental animal, a state resembling secondary shock with lowered blood pressure supervenes (Davis<sup>25</sup>).

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14. Gürber, A.: Die Gesamtzahl der Blutkörperchen und ihre Variation, Arch. f. d. ges. Physiol. **1**:83-95, 1889.

15. Utheim, K.: A Study of the Blood and Its Circulation in Normal Infants and in Infants Suffering from Chronic Nutritional Disturbances, Am. J. Dis. Child. **20**:366-392 (Nov.) 1920.

16. Salge, B.: Ueber die physikalischen Eigenschaften des Blutes des Säuglings, Ztschr. f. Kinderh. **2**:347-359, 1911.

17. Keith, N. M.: Circulatory Changes in Experimental Dehydration, Am. J. Physiol. **63**:394-395, 1923.

18. Howland, J., and Marriott, W. McK.: Acidosis Occurring with Diarrhea, Am. J. Dis. Child. **11**:309-325 (May) 1916.

19. Schloss, O. M., and Stetson, R. E.: The Occurrence of Acidosis with Severe Diarrhea, Am. J. Dis. Child. **13**:218-230 (March) 1917.

20. Clausen, S. W., cited by Marriott.<sup>10</sup>

21. Sellards, A. W., and Shakklee, A. O.: Indications of Acid Intoxication in Asiatic Cholera, Philippine J. Sc. **6**:53-76, 1911.

22. Rogers, L.: The Treatment of Cholera by Injections of Hypertonic Saline Solutions with a Simple and Rapid Method of Intra-Abdominal Administration, Philippine J. Sc. **4**:99-105, 1909.

23. McCulloch, H.: Studies on the Heart in Nutritional Disturbances in Infancy, Am. J. Dis. Child. **20**:486 (Dec.) 1920.

24. Feilchenfeld, W.: Ueber Oertel's Heilverfahren mittelst Flüssigkeitsentziehung mit besonderer Berücksichtigung des Einflusses auf die Diurese, Ztschr. f. klin. Med. **11**:403-436, 1886.

The tissue lesions of acute anhydremia are of interest and consist of widespread capillary distention with numerous petechial hemorrhages into the pulmonary alveoli, the subendocardium, the spleen, the leptomeninx and elsewhere. The adrenal glands may show petechial hemorrhages in the cortices and dense infiltration with polymorphonuclear leukocytes (Davis<sup>25</sup>). The question now raises itself: How much loss of water will the body tolerate before death occurs? It is evident that rapidity of loss of water is the most important factor in determining the outcome. In dogs, death will result when an amount of water equivalent to 4 per cent of the body weight is lost rapidly (Davis<sup>27</sup>).

*Measurement of Degree of Dehydration.*—The methods of determining the degree of dehydration may now be discussed briefly. The clinical manifestations are obvious. The skin becomes wrinkled and dry, and the mucous membranes are lusterless. The eyeballs become soft. As a result of the deficient flow of blood, the extremities are cold. The respirations may be deep and of the "air hunger" type due to acidosis. Various other tests of hydration may be used:

1. Those applicable to the skin:
  - (a) Standard wheal formation (Ebbecke;<sup>28</sup> Pilcher<sup>29</sup>)
  - (b) Intradermal salt absorption (Aldrich and McClure<sup>30</sup>)
  - (c) Intradermal serum absorption (Ribadeau-Dumas and Tisserand<sup>31</sup>)
2. Those applicable to the blood:
  - (a) Erythrocyte concentration (Schade and Menschel<sup>32</sup>)
  - (b) Hemoglobin concentration (Greene and Rowntree<sup>33</sup>)

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25. Davis, H. A.: Acute Circulatory Failure (Shock) Following the Subcutaneous Injection of Hypertonic Sodium Chloride Solution, *Proc. Soc. Exper. Biol. & Med.* **43**:354-357, 1940.

26. Davis, H. A.: Lesions of the Tissues in Dehydration Shock, *Proc. Am. Soc. Exper. Path.*, March 1940, p. 20.

27. Davis, H. A.: Relative Significance of Water and of Protein Loss in Dehydration Shock, *Proc. Soc. Exper. Biol. & Med.* **43**:357-359, 1940.

28. Ebbecke, U.: Capillarerweiterung, Urticaria und Schock, *Klin. Wochenschr.* **2**:1725-1727, 1923.

29. Pilcher, J. D.: Wheal Formation in Infants and Children in Edema, Cretinism, Scleredema, Sclerema, Nephritis, Cardiac Disease, Severe Prostration, and Tuberculin Positive Subjects, *Am. J. Dis. Child.* **31**:77-95 (Jan.) 1926.

30. Aldrich, C. A., and McClure, W. B.: Intradermal Salt Solution Test: Its Prognostic Value in "Nephritis" with Generalized Edema, *J. A. M. A.* **82**:1425-1428 (May 3) 1924.

31. Ribadeau-Dumas, L., and Tisserand, D.: Etude sur la résorption des sérums chez les infants atteints d'affections diverses avec dénutrition, *Bull. et mém. Soc. méd. d. hôp. de Paris* **49**:1637-1641, 1925.

32. Schade, H., and Menschel, H.: Ueber die Gesetze der Gewebsquellung und ihre Bedeutung für klinische Frage (Wasseraustausch im Gewebe, Lymphbildung und Oedementstehung), *Ztschr. f. klin. Med.* **96**:279-327, 1923.

- (c) Hematocrit reading (Dresel and Leitner <sup>34</sup>)
- (d) Specific gravity of the blood plasma (Moore and Stewart <sup>35</sup>)
- 3. Response to administration of water in terms of:
  - (a) Excretion of urine (Volhard <sup>36</sup>)
  - (b) Time curve of blood dilution (Rominger;<sup>5</sup> Davis <sup>37</sup>)
  - (c) Rate of oxygen consumption (Davis <sup>38</sup>)

In practice one will find that the tests of group 3 provide the most comprehensive picture of the state of the dehydrated patient. The accuracy of the Volhard test will depend on the presence of normal renal function. The fact that in the presence of the severer grades of dehydration a fall in hemoconcentration and in the amount of plasma proteins occurs is a justifiable basis for criticism of the tests of group 2. Moreover, losses of blood occurring during surgical operations will further invalidate such tests. Recently, Hopps and Christopher <sup>39</sup> have reported encouraging results with the McClure-Aldrich test in the estimation of dehydration in surgical patients.

*Fluid Replacement in Cases of Dehydration.*—It might be pointed out that our discussion at this point will refer only to that form of dehydration which is uncomplicated by gross losses of electrolytes or of blood. Minor grades of dehydration may be treated by water administered by the oral or the rectal route. However, many dehydrated patients require treatment with fluids given intravenously. The response of the dehydrated organism to intravenous fluids must be given consideration (chart 1). The administration of isotonic dextrose solutions leads to a marked increase in the metabolic rate and in oxygen utilization. Coincidentally there occurs an increased breakdown of protein, as evidenced

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33. Greene, C. H., and Rowntree, L. G.: Effect of Experimental Administration of Excessive Amounts of Water on Volume and Concentration of Blood, *Am. J. Physiol.* **80**:209-229, 1927.

34. Dresel, K., and Leitner, Z.: Zur Physiologie und funktionellen Pathologie des Wasserhaushaltes; die Beziehungen der Milz zum Wasserhaushalt, *Ztschr. f. klin. Med.* **111**:394-419, 1929.

35. Moore, N. S., and Stewart, H. J.: Variations of Specific Gravity of Plasma of Blood and Means Available for Altering It, *J. Clin. Investigation* **9**: 423-442, 1930.

36. Volhard, F., in von Bergmann, G., and Staehelin, R.: *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1931, vol. 2, p. 1023.

37. Davis, H. A.: Behavior of Isotonic and Hypertonic Solutions in Blood Stream of Normal and Dehydrated Animals, *Proc. Soc. Exper. Biol. & Med.* **32**:210-211, 1934.

38. Davis, H. A.: Studies in Water Balance: Excessive Oxygen Usage Response of Dehydrated Animals to Water and Electrolytes, *Proc. Soc. Exper. Biol. & Med.* **33**:242-244, 1935.

39. Hopps, H. C., and Christopher, F.: The McClure-Aldrich Test in Water Balance Following Operation, *Surg., Gynec. & Obst.* **69**:637-644, 1939.

by the augmented output of nitrogenous products in the urine. Intravenous administration of isotonic sodium chloride solution is followed by only a moderate increase in the metabolic rate (Davis<sup>38</sup>). Using these facts as a basis in the replacement therapy of dehydration, we customarily divide dehydrated patients into three groups:

1. Patients showing dehydration with mild anhydremia.
2. Patients showing dehydration with severe anhydremia.
3. Patients with dehydration shock.

The first group comprises those patients who, while exhibiting the usual clinical evidences of dehydration, do not have any lowering of the blood pressure and whose blood reveals an erythrocyte count not exceeding 5,000,000 per cubic millimeter. When fluid replacement by the parenteral route is indicated, one may administer 2,500 cc. of 5 per cent dextrose solution by vein each twenty-four hours until the

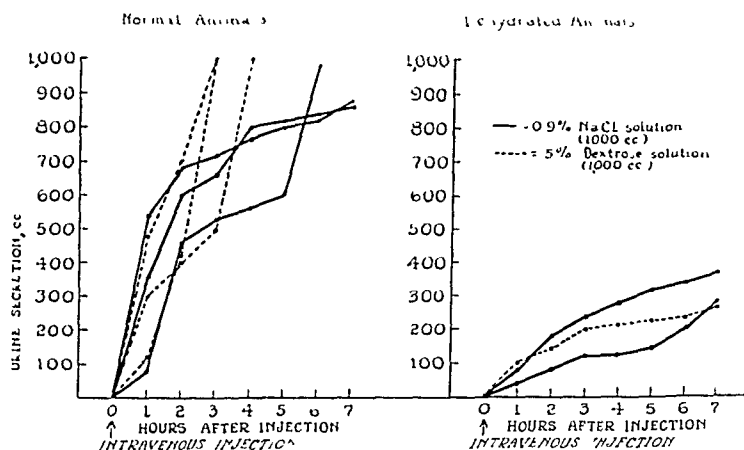


Chart 1.—Differential response of normal and dehydrated animals to water and electrolytes.

output of urine reaches 1,000 cc. daily. The dextrose is readily oxidized, releasing the water for purposes of vaporization from the lungs and skin and for urine formation.

Patients falling into the second group exhibit erythrocyte counts exceeding 5,000,000 per cubic millimeter of blood and some lowering of the systolic blood pressure. Five per cent dextrose solution is used, but only 1,000 cc. is administered in the first twenty-four hours, 1,500 cc. in the second twenty-four hours and 2,000 cc. in the third twenty-four hours. Thereafter, 2,500 cc. is given daily until the volume of urine reaches 1,000 cc. per day. It is essential that the solution be administered slowly, at a rate of 4 to 5 cc. per minute, as the concentrated blood holds the injected fluid for a long period, and, as a result there is present a definite danger of overdistention of the right side of the heart.

In the third group may be placed those persons who manifest the more severe secondary effects of dehydration, namely, anhydremia, reduced blood volume, acidosis, lowering of the oxygen content of the blood, hyperglycemia, diminished volume flow of blood and reduction of the systolic blood pressure. Some of these patients will exhibit symptoms of secondary shock. The blood is concentrated. However, in the later stages there may occur a breakdown of the red blood cells and of the plasma proteins, so that hemoconcentration may be slight or absent. It has been pointed out that pulmonary edema occurs in cases of shock associated with dehydration (Davis<sup>26</sup>). Crystalloid solutions administered by vein at this time will not be retained by the blood but will pass out into the extravascular tissue spaces. Moreover, such solutions will favor an increase of the pulmonary edema. It is apparent that the essential treatment at this point should be directed toward restoring the blood volume. This may be accomplished by preliminary transfusions of whole blood, plasma or ascitic fluid (Davis and White<sup>40</sup>). Thereafter, fluid replacement may proceed along the lines indicated for the patients of group 2. It may be questioned whether electrolyte replacement should be undertaken in the presence of dehydrated states. While there occurs some loss of sodium, potassium and chloride ions (Tobler;<sup>4</sup> Meyer<sup>41</sup>), restitution may be deferred until hydration has been partially accomplished by means of isotonic dextrose solutions.

#### LOSS OF ELECTROLYTES

The total water content of the body is directly proportional to the number of osmotically active particles present in the tissues. The major portion of these particles is electrolytes. It has been demonstrated by many workers (Gamble and Ross;<sup>42</sup> Gamble and McIver<sup>43</sup>) that sodium is the most important electrolyte in the maintenance of normal osmotic relations between the extracellular and the intracellular fluids. The daily intake of salt varies from 3 to 10 Gm.; of which 1 to 2 Gm. is derived from food. Approximately 0.2 Gm. of sodium chloride is lost per day in the stools (Welch, Masson and Wakefield<sup>44</sup>) and 0.25 to 0.41 Gm.

40. Davis, H. A., and White, C. S.: Human Ascitic Fluid as a Blood Substitute in Experimental Secondary Shock, *Proc. Soc. Exper. Biol. & Med.* **38**: 462-465, 1938.

41. Meyer, L. F.: Ueber den Wasserbedarf des Säuglings, *Ztschr. f. Kinderh.* **5**:1-30, 1912.

42. Gamble, J. L., and Ross, S. G.: Factors in Dehydration Following Pyloric Obstruction, *J. Clin. Investigation* **1**:403-423, 1925.

43. Gamble, J. L., and McIver, M. A.: Acid-Base Composition of Gastric Secretion, *J. Exper. Med.* **48**:837-847, 1928.

44. Welch, C. S.; Masson, J. C., and Wakefield, E. G.: Clinical and Laboratory Findings After Excessive Loss of Intestinal Fluid from the Ileum, *Surg., Gynec. & Obst.* **64**:617-621, 1937.

by insensible perspiration (Freyberg and Grant <sup>45</sup>), while the remaining excess is excreted by the kidneys. The various gastrointestinal secretions contain electrolytes, the basic sodium ion being found in the pancreatic juice and bile and the acidic chloride ion in the gastric juice. Under normal circumstances the electrolytes in these juices are reabsorbed, and thus no loss from the body occurs. However, if failure of reabsorption occurs, as it does in certain surgical conditions, a therapeutic problem arises. In clinical states, loss of water usually accompanies loss of electrolytes. It is not this loss of water which is significant but rather the fact that as the total amount of electrolytes diminishes the ability of the organism to retain water decreases proportionately.

*Physiologic Effects of Loss of Electrolytes.*—It is necessary to distinguish the effects of loss of electrolytes per se from those of secondary dehydration. In animals in which a loss of electrolytes is produced by means of a gastric fistula (Dragstedt and Ellis <sup>46</sup>) or by means of a pancreatic fistula (Dragstedt, Montgomery and Ellis <sup>47</sup>), there occur gradually increasing muscular weakness, loss of appetite and a tendency to muscular tremors. Terminal convulsions may occur. If sodium mainly is lost, acidosis occurs, and if chloride is lost, alkalosis develops. Other phenomena, such as hemoconcentration, decrease in the output of urine and diminution in the amount of gastric and pancreatic juice secreted, may be attributed to secondary dehydration. In man the rapid loss of electrolytes results in muscular cramps and fatigue. The effects of the gradual loss of electrolytes in man have been investigated by McCance <sup>48</sup> and others. Anorexia, nausea and a tendency toward muscular fatigue and cramps were prominent symptoms. Mental fatigue, inability to concentrate and slowness of mental reactions were noted. There was a fall in the level of plasma and corpuscular chlorides and in that of serum sodium, with an increase in the level of serum potassium. The blood pressure was unchanged in spite of a presumptive reduction of the blood volume as evidenced by hemoconcentration. While these changes comprised the effects of loss of salt, others, equally definite, could be attributed to the resultant dehydration. Among the latter were severe loss of weight, hemoconcentration with respect to erythrocytes and hemoglobin, increase in plasma proteins and blood urea and a nega-

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45. Freyberg, R. H., and Grant, R. L.: Loss of Minerals Through the Skin of Normal Humans When Sweating Is Avoided, *J. Clin. Investigation* **16**:729-731, 1937.

46. Dragstedt, L. R., and Ellis, J. C.: Fatal Effect of Total Loss of Gastric Juice, *Am. J. Physiol.* **93**:407-410, 1930.

47. Dragstedt, L. R.; Montgomery, M. L., and Ellis, J. C.: New Type of Pancreatic Fistula, *Proc. Soc. Exper. Biol. & Med.* **28**:109-110, 1930.

48. McCance, R. A.: Medical Problems in Mineral Metabolism: Experimental Human Salt Deficiency, *Lancet* **1**:823-830, 1936.

tive nitrogen balance. It is apparent, therefore, that the sequence of events initiated by loss of electrolytes, particularly sodium, ends in dehydration with anhydremia, progressive reduction of the blood volume and, finally, generalized anoxemia, shock and death.

*Surgical Causes of Loss of Electrolytes.*—While as much as 2 Gm. of salt may be lost each hour in the perspiration when sweating is excessive (Dill, Jones, Edwards and Oberg<sup>49</sup>), this is not a common source of depletion in surgical patients. More common, however, is a loss of electrolytes via the gastrointestinal secretions. Vomiting due to obstruction of various portions of the alimentary canal results in loss of gastric juice, succus entericus, pancreatic juice or bile. The predominant electrolyte in gastric juice is the chloride ion, and loss of this results in hypochloremia and alkalosis. In bile, pancreatic juice and succus entericus the principal electrolyte is sodium, and loss of this ion is followed by acidosis. The production of artificial openings in the intestinal tract, e. g., by jejunostomy, ileostomy or cecostomy, may result in a considerable loss of unabsorbed electrolytes. Prolonged drainage from a biliary fistula may lead to extensive depletion of the sodium ion and to acidosis. Similarly, prolonged diarrhea, in which the electrolytes are removed from the body before reabsorption occurs, leads to loss of the sodium ion and to acidosis. The loss of electrolytes in the discharges from suppurating wounds may be significant. In addition, prolonged use of Wangensteen or Miller-Abbott gastrointestinal tubes may result in severe depletion of water and electrolytes.

*Measurement of Degree of Electrolyte Loss.*—The degree of loss of electrolytes may be determined either directly or indirectly. Estimation of the level of plasma sodium chloride, which varies normally from 560 to 630 mg. per hundred cubic centimeters of blood, gives a direct clue to the extent of electrolyte loss. A study of the secondary effects of electrolyte loss provides an indirect method of evaluating its extent. This may be done in two ways:

1. Estimation of the carbon dioxide-combining power of the plasma.
2. Estimation of the degree of secondary dehydration by means of blood studies, erythrocyte count, hemoglobin determination, etc.

When the basic ions, such as sodium, are lost, acidosis results, and the carbon dioxide-combining power of the plasma falls to or below 50 volumes per cent.

Conversely, if a depletion of the acidic ions, such as the chlorides, occurs, alkalosis develops, and the carbon dioxide-combining power of

<sup>49</sup> Dill, D. B.; Jones, B. F.; Edwards, H. T., and Oberg, S. A.: Salt Economy in Extreme Dry Heat, *J. Biol. Chem.* **100**:755-767, 1933.

the plasma is elevated to or above 70 volumes per cent. The methods of determining the grade of secondary dehydration have been discussed previously and will be only mentioned at this point.

*Fluid Replacement.*—The therapeutic problem with patients suffering from loss of electrolytes centers around the resultant dehydration, as the loss of electrolytes per se is self limited. It is the inability of the salt-depleted organism to retain water, while the output of water continues via the skin, lungs and urine, which leads, finally, to a fatal reduction of the blood volume. Before considering the various replacement fluids, it might be pertinent to discuss briefly the response to fluids of the organism suffering from electrolyte depletion and dehydration (chart 2). Dogs which have been depleted of chlorides and in which alkalosis has developed show an increased ability to retain 5 per cent dextrose solu-

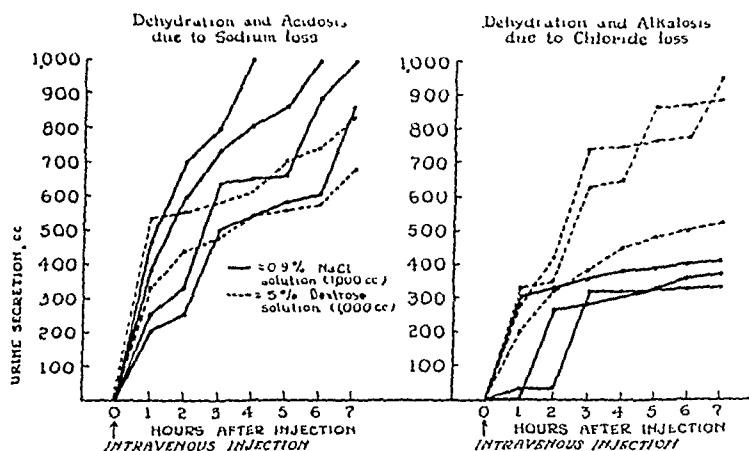


Chart 2.—Differential response of dehydrated animals with acidosis and with alkalosis to water and electrolytes.

tion and 0.9 per cent sodium chloride solution injected intravenously. However, retention of sodium chloride solution is relatively much greater than that of dextrose solution and corresponds with that observed in animals which have been dehydrated by deprivation of water. On the other hand, animals which have suffered a loss of sodium base resulting in dehydration with acidosis reveal an incapacity to retain either isotonic dextrose or sodium chloride solution given by vein. The rate of escape of water from such an animal is subject to some interesting variations. When an extensive loss of basic ions has occurred and fluid replacement takes the form of administration of 5 per cent dextrose solutions, the administration of isotonic solution of sodium chloride may precipitate a diuresis (Davis and Dragstedt<sup>50</sup>). The explanation of this paradoxical

50. Davis, H. A., and Dragstedt, L. R.: The Relative Significance of Electrolyte Concentration and Tissue Reaction in Water Metabolism, *Am. J. Physiol.* **113**:193-199, 1935.



phenomenon may be that the loss of base is such that the body fluids become relatively hypotonic. Physiologic solution of sodium chloride is then hypertonic with respect to the body fluids and when administered provokes a flow of interstitial fluid into the blood vessels and an increased output of urine.

Somewhat analogous results were obtained by McCance and his associates in human beings suffering from loss of sodium. In such persons

TABLE 1.—Types of Blood Substitutes

- 
- A. Whole or Partial Blood
- (a) Fresh
1. Whole blood } Donors
  2. Citrated blood } Autotransfusion
  3. Blood plasma or serum
  4. Defibrinated blood
- (b) Preserved
1. Living donor's blood
  2. Placental blood
  3. Cadaver blood
  4. Blood plasma and serum
  5. Human ascitic fluid
  6. "Lyophile" plasma and serum
  7. "Lyophile" ascitic fluid
  8. Hemoglobin in Ringer's solution
- B. Artificial Substitutes for Blood
1. Acacia in saline solution
  2. Gelatin-saline solution
  3. Amino acid solution
  4. Isotonic dextrose solution
  5. Modifications of electrolyte solutions:
    - (a) Isotonic sodium chloride solution (0.85%)
    - (b) Ringer's solution \*
    - (c) Ringer-Locke's solution †
    - (d) Tyrode solution ‡
    - (e) Normet's solution §
    - (f) Hartmann-Senn solution ¶
    - (g) Dextrose-saline solution
- 

\* Ringer's solution: 0.95% sodium chloride, 0.02% potassium chloride, 0.02% calcium chloride.

† Ringer-Locke solution: 0.9% sodium chloride, 0.042% potassium chloride, 0.024% calcium chloride, 0.1% dextrose, 0.2% sodium bicarbonate, saturated with oxygen.

‡ Tyrode solution: 0.8% sodium chloride, 0.02% potassium chloride, 0.02% calcium chloride, 0.01% magnesium chloride, 0.005% sodium dihydrogen phosphate, 0.1% sodium bicarbonate, 0.1% dextrose.

§ Normet's solution: 22 Gm. of sodium citrate, 6.5 Gm. of neutral calcium citrate, 4.5 Gm. of neutral magnesium citrate, 1 Gm. of iron ammonium citrate, 0.15 Gm. of manganese citrate, 1,000 cc. distilled water; 20 cc. of this mixture to 1,000 cc. 0.7% sodium chloride solution.

¶ Hartmann-Senn solution: 100 cc. 85% lactic acid solution, 700 cc. distilled water; sufficient concentrated sodium hydroxide to make the solution alkaline; distilled water to 1,000 cc.

the diuresis following the ingestion of water was greatly delayed. In addition, the ingestion of salt caused at first a loss of body water and a decrease in weight. It is evident that such abnormal responses to administration of salt and water to sodium-depleted persons must be considered in treatment by replacement of water and electrolytes.

The use of hypertonic solutions of electrolytes is contraindicated, for the reasons already given. Various types of isotonic electrolyte solutions are available (table 1). Coller and Maddock<sup>51</sup> have expressed

51. Coller, F. A., and Maddock, W. G.: The Water Requirements of Surgical Patients. *Ann. Surg.* 98:952-960, 1933.

preference for Ringer's solution. Hartmann and others<sup>52</sup> recommended a solution containing sodium lactate. The lactate is oxidized, leaving the base free. We have found that an isotonic solution of 5 per cent dextrose with 0.9 per cent sodium chloride provides an excellent replacement fluid. The estimated abnormal electrolyte loss plus the basic electrolyte requirement provides a clue to the amount of solution to be administered. The general principles of fluid replacement for this group of patients are similar to those obtaining in cases of dehydration without electrolyte loss. Again, emphasis must be placed on the secondary dehydration. If this has reached the stage of reduction of blood volume, the primary treatment is directed toward its restoration to a normal level by means of blood transfusion or, better still, by plasma or ascitic fluid transfusion. Thereafter, electrolyte solutions may be administered. If the possibility of secondary reduction of the plasma volume and of the plasma proteins as a result of dehydration is not given consideration, injection of electrolyte solutions even in moderate amounts may be followed by edema. This is well illustrated by case 1.

CASE 1.—A white man aged 74 years was admitted to the Charity Hospital of Louisiana at New Orleans suffering from a carcinoma of the esophagus. Extreme dehydration and anhydremia were present, associated with hemoconcentration and increased concentration of the plasma proteins. Fluid replacement by vein was begun, 2,500 cc. of 5 per cent dextrose in 0.9 per cent sodium chloride solution being used daily. On the third day edema of the lower extremities developed, and bubbling rales could be auscultated at the bases of both lungs. It is evident that in this patient there was a diminution in the plasma volume and in the total amount of plasma proteins, in spite of their apparent concentration.

The type of electrolyte lost has an important bearing on the therapeutic problem in this group of cases. When sodium is lost, with resultant acidosis and dehydration, relatively larger amounts of solutions of electrolytes may be administered, as neither the electrolytes nor the water will be well retained, and there is less danger of retention edema. The adjunct use of desoxycorticosterone acetate will help to fix the sodium and, consequently, the water in the tissues. With loss confined mainly to the chloride ion and resulting in alkalosis and dehydration, relatively smaller amounts of electrolyte solutions may be given, as both water retention and electrolyte retention are greater (Davis and Dragstedt<sup>50</sup>).

#### LOSS OF WHOLE BLOOD

Whole blood may be lost externally, into body cavities and into tissues. The causes of such loss are too well known to require enumeration here. The physiologic effects are dependent on the ensuing reduction of the blood volume. The removal of 500 cc. of blood has little

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52. Hartmann, A. F.; Senn, M. J. E.; Nelson, M. V., and Perley, A. M.: Use of Acacia in Treatment of Edema, *J. A. M. A.* **100**:251-254 (Jan. 28) 1933.

effect on the blood pressure, and the blood volume is restored within one hour. The loss of 1,000 cc. of blood or more is usually followed by a fall of blood pressure. Recovery is possible after losses up to 30 per cent of the blood volume. Beyond 30 per cent the ability of the organism to restore the lost volume of blood is insufficient, and death results. The immediate effects of hemorrhage are an increase in the heart rate and the respiratory rate, contraction of the spleen and generalized vasoconstriction. A regional redistribution of blood follows hemorrhage (Davis and Jermstad<sup>53</sup>). Owing to marked constriction of the blood vessels in the splanchnic area, an outflow of blood from that area takes place toward the thoracic region. As a result of the reduced blood volume, a diminution of the volume flow of blood and of the metabolic rate develops. The various elements of the lost blood are replaced at differing rates. Water passes rapidly from the interstitial tissue spaces into the blood stream in order to increase the blood volume. This water contains relatively little protein, so that protein regeneration, which is dependent on the liver, takes several days to be completed. The cellular element is the last to be restored, the erythrocytes not regaining their normal numbers until several weeks have passed.

*Measurement of the Degree of Blood Loss.*—The extent of loss of blood may be gaged approximately by noting the clinical manifestations and by making determinations of the values for erythrocytes, hemoglobin and blood pressure. These are too well known to require elaboration here.

*Fluid Replacement.*—Various fluids have been advocated for replacement of blood. It is obvious that fresh whole blood is the most efficacious fluid. However, this is expensive, is not always available and is incapable of storage beyond three weeks. As a result, a search for an efficient substitute for whole blood has developed. An ideal substitute for blood should possess the following properties:

1. It should be readily available.
2. It should be effective.
3. It should be capable of prolonged storage without deteriorating.
4. It should be nontoxic even when administered in large quantities.
5. It should contain one or more of the elements of blood.
6. It should possess one or more of the biologic properties of blood; for example, ability to transport oxygen or ability to maintain the colloidal osmotic pressure.

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53. Davis, H. A., and Jermstad, R. J.: Regional Redistribution of Blood in Experimental Secondary Shock, Arch. Surg. 38:556-580 (March) 1939.

One may apply these criteria to the fluids which have been advocated for use as blood substitutes (table 1).

**Crystalloid Solutions:** It is apparent that crystalloid solutions cannot be regarded as adequate substitutes for blood, since they do not contain either proteins or hemoglobin. However, in circumstances in which the loss of blood has not been excessive they may exert a favorable influence. When the reduction in blood volume has existed long enough to produce, through oxygen lack, increased permeability of the capillary walls, administration of such solutions may result in a further loss of plasma proteins from the blood stream (Beard and Blalock;<sup>54</sup> Davis<sup>55</sup>) and a reduction in the utilization of oxygen by the organism (Davis<sup>55</sup>). Much disagreement exists regarding the value of crystalloid solutions in the treatment of hemorrhage. MacFee and Baldrige<sup>56</sup> and Hoitink<sup>57</sup> have stated that such solutions are useful, while others have expressed the opposite opinion. This difference of opinion would disappear if it were recognized that it is the factor of capillary permeability which determines the degree of efficacy of such solutions (chart 3). The crystalloid-containing fluids which have been recommended for use are given in table 1. It is possible that certain of the beneficial effects of such fluids can be attributed to their action on the cardiovascular system. Normet's<sup>58</sup> fluid (table 1) contains various citrates which not only stimulate the heart but cause vasoconstriction. In Hartmann-Senn solution (table 1) there is present sodium R-lactate, which acts as a buffer and helps to overcome either alkalosis or acidosis. In animals, administration of crystalloid solutions in excessive amounts results in pulmonary edema (Davis<sup>55</sup>). This fact should be remembered when such fluids are administered to patients suffering from loss of whole blood with resultant alteration of capillary permeability.

**Acacia Solution:** While solutions of acacia were injected into animals as early as 1881, their first deliberate use as fluids for replacement

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54. Beard, J. W., and Blalock, A.: *Intravenous Injections: A Study of the Composition of the Blood During Continuous Trauma to the Intestines When No Fluid Is Injected and When Fluid Is Injected Continuously*, J. Clin. Investigation **11**:249-265, 1932.

55. Davis, H. A.: *Physiological Availability of Fluids in Secondary Shock*, Arch. Surg. **35**:461-477 (Sept.) 1937.

56. MacFee, W. F., and Baldrige, R. R.: *Post-Operative Shock and Shock-Like Conditions: Treatment by Infusion in Large Volumes*, Ann. Surg. **91**:329-341, 1930.

57. Hoitink, A. W. J. H.: *Treatment of Acute Fatal Hemorrhage by Injection of Artificial Blood Substitutes*, Surg., Gynec. & Obst. **61**:613-622, 1935.

58. Normet, L.: *Traitement des hémorragies expérimentales chez le chien par un sérum artificiel à base de citrates*, Compt. rend. Acad. d. sc. **188**:354-356, 1929.

of blood after hemorrhage did not take place until 1906 (Morawitz<sup>59</sup>). Since that time various investigators have shown that acacia solutions (6 per cent in 0.9 per cent sodium chloride or 5 per cent dextrose solutions) are capable of raising the blood pressure and maintaining the blood volume after hemorrhage (Bayliss<sup>60</sup>). Unsatisfactory results have been reported, however, with acacia solutions after loss of blood (Kruse;<sup>61</sup> Henderson and Haggard;<sup>62</sup> Tsurumaki and Kurozawa<sup>63</sup>). The permeability of the capillaries increases when the low blood pressure following loss of blood is allowed to persist. The presence of this factor may influence the results obtained and may explain the observations of Penfield,<sup>64</sup> who noted that acacia solutions were not more effective in saving shocked animals than was isotonic solution of sodium

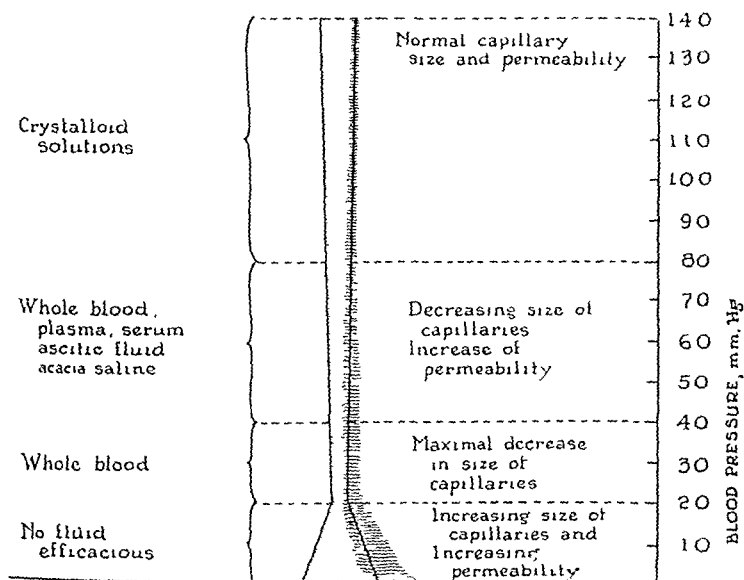


Chart 3.—Shock due to loss of whole blood; efficacy of replacement fluids in relation to capillary permeability.

59. Morawitz, P.: Ueber einige postmortale Blutveränderungen, Beitr. z. Physiol. **8**:1-14, 1906.

60. Bayliss, W. M.: The Use of Gum Solutions for Intravenous Injection, Brit. M. J. **1**:564, 1917.

61. Kruse, T. K.: The Pharmacology of Acacia, Am. J. Physiol. **49**:137, 1919.

62. Henderson, Y., and Haggard, W. H.: Hemorrhage as a Form of Asphyxia, J. A. M. A. **78**:697-704 (March 11) 1922.

63. Tsurumaki, T., and Kurozawa, R.: Intravenous Infusion of Physiological Salt and Ringer-Locke's Solution Containing Gum Arabic, Acta scholae med. univ. imp. in Kioto **6**:471-497, 1924.

64. Penfield, W. G.: Treatment of Severe and Progressive Hemorrhage by Intravenous Injections, Am. J. Physiol. **48**:121, 1919.

chloride. Hurwitz<sup>65</sup> was the first to administer acacia solutions to human beings. His work was followed by that of Bayliss,<sup>66</sup> Coburn and Ward<sup>66</sup> and Good, Mugrage and Weiskittel,<sup>67</sup> all of whom reported the successful use of such solutions.

Acacia solutions, nevertheless, are not devoid of toxicity. Deaths have followed their use (Lee<sup>68</sup>). Anaphylactic reactions to acacia occur in man and in guinea pigs (Maytum and Magath<sup>69</sup>). Acacia solutions in vitro produce agglutination of the red blood cells (Lucia and Brown<sup>70</sup>). They may also lower the oxygen content of the blood by coating the red blood cells (Christie, Phatak and Olney<sup>71</sup>). The last-mentioned fact may render their use dangerous when the red cell count has been reduced to very low levels by hemorrhage. Acacia is engulfed by the cells of the reticuloendothelial system and may remain in the body for months (Andersch and Gibson<sup>72</sup>) or even for years (Keith, Power and Wakefield<sup>73</sup>). Regeneration of plasma proteins by the liver is interfered with, and repeated injections of acacia solutions may lead to hypoproteinemia (Dick, Warweg and Andersch<sup>74</sup>). Finally, it has been demonstrated that acacia solutions leave the blood stream fairly readily and cannot maintain the osmotic pressure of the blood for more than forty-eight hours (Huffman<sup>75</sup>). Each of the fluids

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65. Hurwitz, S. H.: *Acacia Solutions*, J. A. M. A. **68**:699 (March 3) 1917.

66. Coburn, R. C., and Ward, G. G.: *Blood Pressure in Operative Surgery and General Anesthesia with Especial Reference to the Use of Gum Glucose*, S. Clin. North America **5**:548-553, 1925.

67. Good, R. W.; Mugrage, R., and Weiskittel, R.: *Acacia Solution in Treatment of Surgical Shock: Analysis of One Hundred and Eleven Case Histories*, Am. J. Surg. **25**:134-139, 1934.

68. Lee, R. Van A.: *Sudden Death in Two Patients Following Intravenous Injection of Acacia*, J. A. M. A. **79**:726-728 (Aug. 26) 1922.

69. Maytum, C. K., and Magath, T. B.: *Sensitivity to Acacia*, J. A. M. A. **99**:2251-2252 (Dec. 31) 1932.

70. Lucia, S. P., and Brown, J. W.: *Suspension Stability of Erythrocytes in Solution of Gum Acacia*, Proc. Soc. Exper. Biol. & Med. **32**:189-192, 1934.

71. Christie, A.; Phatak, N. M., and Olney, M. B.: *Effect of Intravenous Acacia on Physico-Chemical Properties of Blood*, Proc. Soc. Exper. Biol. & Med. **32**:670-672, 1935.

72. Andersch, M., and Gibson, R. B.: *Studies on Effects of Intravenous Injections of Colloids: Deposition of Acacia in Liver and Other Organs and Its Excretion in Urine and Bile*, J. Pharmacol. & Exper. Therap. **52**:390-407, 1934.

73. Keith, N. M.; Power, M. H., and Wakefield, E. G.: *Detection and Persistence of Acacia in Blood*, Proc. Staff Meet, Mayo Clin. **10**:38-41, 1935.

74. Dick, M. W.; Warweg, E., and Andersch, M.: *Acacia in Treatment of Nephrosis*, J. A. M. A. **105**:654-657 (Aug. 31) 1935.

75. Huffman, L. D.: *Solution of Acacia and Sodium Chloride in Hemorrhage and Shock: Effect of Intravenous Administration*, J. A. M. A. **93**:1698-1702 (Nov. 30) 1929.

discussed has a serious disadvantage, as none possesses any of the normal constituents of blood. The therapeutic problem becomes somewhat clarified when one deals with replacement fluids which contain one or more of these constituents. Those fluids will now be considered.

**Preserved Blood:** The transfusion of preserved blood was first performed by Hédon<sup>76</sup> in 1902. During the World War (1914 to 1918) preserved blood was used in human beings by Robertson.<sup>77</sup> Little was done with this substitute for fresh blood until it was reintroduced by Jeanneney and his co-workers<sup>78</sup> and by Palazzo and Tenconi<sup>79</sup> in 1934. Despite the use of various blood-preservative solutions, such as sodium citrate solution, Rous-Turner solution and I. H. T. solution,<sup>79a</sup> the safe maximal period of preservation of whole blood does not exceed three weeks. The incidence of post-transfusion reactions increases with the period of preservation. In most respects, however, preserved blood retains the biologic properties of fresh blood. There are many difficulties associated with the maintenance of an adequate supply of preserved blood from living donors. For that reason, the use of placental blood has been advocated (Barenboym and Kaplan;<sup>80</sup> Bruskin and Farberova;<sup>81</sup> Goodall and others<sup>82</sup>). However, only 50 to 70 cc. of blood can be obtained from the average placenta, and a high incidence of staphylococcic contamination has been reported (Hawkins and Brewer<sup>83</sup>). Applying to man the experimental work of Shamov<sup>84</sup>

76. Hédon, M.: Transfusion après les hémorrhagies de globules rouges en suspension dans du sérum artificiel, *Arch. de méd. expér.* **14**:297, 1902.

77. Robertson, O. H.: Transfusion with Preserved Red Blood Cells, *Brit. M. J.* **1**:691-695, 1918.

78. Jeanneney, G.; Servantié, L., and Viéroz, J.: Transfusion du sang conservé plusieurs jours en pratique médico-chirurgicale courante, *J. de méd. de Bordeaux* **111**:685-686, 1934.

79. Palazzo, R., and Tenconi, J.: Transfusión de sangre conservada, *Semana méd.* **2**:1179-1193, 1934.

79a. Rous-Turner solution: 3.8 per cent sodium citrate and 5.6 per cent dextrose. I. H. T. solution: 5 Gm. of sodium citrate, 7 Gm. of sodium chloride, 0.2 Gm. of potassium chloride, 0.006 Gm. of magnesium sulfate and 1,000 cc. of distilled water.

80. Barenboym, S. I., and Kaplan, A. V.: Transfusion of Placental Blood: Preliminary Report, *Sovet. khir.* **7**:205-212, 1934.

81. Bruskin, M., and Farberova, P. S.: Use of Umbilical and Placental Blood for Massive Transfusions in Surgical Clinic, *Sovet. vrach. zhur.* **20**:1546-1551, 1936.

82. Goodall, J. R.; Anderson, F. O.; Altimas, G. T., and MacPhail, F. L.: Inexhaustible Source of Blood for Transfusion and Its Preservation: Preliminary Report (on Placental Blood), *Surg., Gynec. & Obst.* **66**:176-178, 1938.

83. Hawkins, J., and Brewer, H. F.: Placental Blood, *Lancet* **1**:132-134, 1939.

84. Shamov, W. N.: Transfusion of Stored Cadaver Blood, *Lancet* **2**:306-309, 1937.

on animals, Judine<sup>85</sup> has utilized the blood obtained from cadavers for transfusion. As much as 1,500 cc. of blood may be obtained from a single cadaver. The incidence of post-transfusion reactions is high—21 per cent—and several fatalities have occurred (Judine and Skundina<sup>86</sup>). In spite of the fact that fresh defibrinated blood is known to be very toxic (Moldovan<sup>87</sup>), Behr<sup>88</sup> has used it for transfusion, reporting a 17 per cent incidence of reactions.

**Hemoglobin in Solution:** The functional value of hemoglobin in solution has been investigated with a view to its possible use for blood replacement. Hemoglobin dissolves readily in isotonic salt solutions and in this form takes up oxygen more rapidly than does intracellular hemoglobin (Hartridge and Roughton<sup>89</sup>). It exerts in solution a definite colloidal osmotic pressure which is greater than that of the plasma proteins (Adair;<sup>90</sup> Wells, Miller and Drake<sup>91</sup>). These facts have induced Amberson and his co-workers<sup>92</sup> to utilize 12 to 14 per cent hemoglobin in Ringer's solution as a replacement fluid for blood. They found that almost complete replacement of blood might be accomplished, the animals exhibiting a normal behavior as long as the hemoglobin concentration was maintained at a high level. When the concentration of hemoglobin fell below 3 per cent, death from asphyxia occurred. This form of extracellular hemoglobin leaves the blood stream quickly and, since it is soon converted into methemoglobin, becomes incapable of carrying oxygen. During the process of excretion the kidneys become the site of deposition of methemoglobin. The use of

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85. Judine, S.: *La transfusion du sang de cadavre à l'homme*, Paris, Masson & Cie, 1933, p. 144.

86. Judine, S., and Skundina, G.: *Das Problem der Leichenbluttransfusion*, Wien. med. Wchnschr. **84**:817-822, 1934.

87. Moldovan, J.: *Ueber die Wirkung intravaskulärer Injektionen frischen, defibrinierten Blutes und ihre Beziehungen zur Frage der Transfusion*, Deutsche med. Wchnschr. **36**:2422-2425, 1910.

88. Behr, W.: *Unsere Erfahrungen mit der Übertragung defibrinierten Blutes*, Med. Klin. **29**:156-157, 1933.

89. Hartridge, H., and Roughton, F. J. W.: *Rate of Distribution of Dissolved Gases Between Red Blood Corpuscles and Its Fluid Environment: Preliminary Experiments on Rate of Uptake of Oxygen and Carbon Monoxide by Sheep's Corpuscles*, J. Physiol. **62**:232-242, 1927.

90. Adair, G. S.: *Hemoglobin System: Reproduction of Carbon Dioxide Curves of Blood with an Artificial Mixture of Hemoglobin and Sodium Bicarbonate*, J. Biol. Chem. **63**:515-516, 1925.

91. Wells, H. S.; Miller, D. G., Jr., and Drake, B. M.: *Validity of Rapid Determinations of Osmotic Pressure of Protein Solutions*, J. Clin. Investigation **14**:1-6, 1935.

92. Amberson, W. R.; Mulder, A. G.; Steggerda, F. R.; Flexner, J., and Pankratz, D. S.: *Mammalian Life Without Red Corpuscles*, Science **78**:106-107, 1933.



5 per cent hemoglobin in Ringer's solution for human beings has been attended by severe reactions (O'Shaughnessy and others<sup>93</sup>). It is evident that hemoglobin in solution does not represent, at its present stage of development, a practical blood replacement fluid.

**Blood Plasma and Blood Serum:** Although both blood plasma and blood serum contain vasopressor (Bayliss and Ogden<sup>94</sup>) and vasodepressor (Stewart and Harvey;<sup>95</sup> Freund<sup>96</sup>) substances, this fact has not prevented their use as blood replacement fluids. Despite the lack of hemoglobin, the physiologic availability of plasma and serum as substitutes for blood after hemorrhage has been demonstrated in animals (Guthrie and Pike;<sup>97</sup> Rossius;<sup>98</sup> Kallius<sup>99</sup>). Plasma apparently is more efficacious than serum (Richet, Brodin and Saint-Girons<sup>100</sup>). Plasma transfusions in human beings have been used for purposes of hemostasis (Burceva<sup>101</sup>), for hemorrhagic shock (Filatov and Kartaševskij<sup>102</sup>), for traumatic shock (Filatov and Kartaševskij<sup>102</sup>) and for hemolytic shock (Heinatz and Sokolow<sup>103</sup>). The incidence of post-transfusion reactions has been high, varying from 34 per cent (Burceva<sup>101</sup>) to 67.6 per cent (Alovski and Burceva<sup>104</sup>). The plasma from

93. O'Shaughnessy, L.; Mansell, H. E., and Slome, D.: Haemoglobin Solution as a Blood Substitute, *Lancet* **2**:1068-1069, 1939.

94. Bayliss, L. E., and Ogden, E.: "Vasotonins" and the Pump-Oxygenator-Kidney Preparation, *J. Physiol.* **77**:34-35, 1933.

95. Stewart, H. A., and Harvey, S. C.: The Vasodilator and Vasoconstrictor Properties of Blood Serum and Plasma, *J. Exper. Med.* **16**:103-125, 1912.

96. Freund, H.: Ueber die pharmakologischen Wirkungen des defibrinierten Blutes, *Arch. f. exper. Path. u. Pharmacol.* **86**:266-280, 1920.

97. Guthrie, C. C., and Pike, F. H.: The Relation of the Activity of the Excised Mammalian Heart to Pressure in the Coronary Vessels and to Its Nutrition, *Am. J. Physiol.* **18**:14-38, 1907.

98. Rossius, L.: Ein tierexperimentellen Beitrag zur Frage der Bluttransfusion, *Arch. f. klin. Chir.* **137**:583-618, 1925.

99. Kallius, H. U.: Die Verweildauer der gebräuchlichen Blutersatzflüssigkeiten, insbesondere transfundierten Serums nach grossen Blutverlusten im Tierexperiment, *Deutsche Ztschr. f. Chir.* **220**:216-238, 1929.

100. Richet, C.; Brodin, P., and Saint-Girons, F.: Des injections de plasma sanguin (plasmothérapie) pour remplacer le sang total, *Compt. rend. Acad. d. sc.* **167**:618, 1918.

101. Burceva, E.: Transfusion kleiner konservierter Plasmamengen zwecks Blutstillung, *Arch. f. klin. Chir.* **182**:710-717, 1935.

102. Filatov, A., and Kartaševskij, N.: Die Transfusion von menschlichem Blutplasma als blutstillendes Mittel, *Zentralbl. f. Chir.* **62**:441-445, 1935.

103. Heinatz, S. W., and Sokolow, N. I.: Plasmatransfusion als Methode der Wahl in der Behandlung des hämolytischen Schocks, *Zentralbl. f. Chir.* **62**:1753-1755, 1935.

104. Alovski, A., and Burceva, E.: Die Transfusion von konserviertem Blutplasma bei gynäkologischen Blutungen, *Monatschr. f. Geburtsh. u. Gynäk.* **105**:38-46, 1937.

group AB blood does not agglutinate the red blood cells of other blood groups and may be used without preliminary cross-matching tests. Lyophile plasma and serum prepared by the method of Flosdorf and Mudd<sup>105</sup> have been used successfully for replacement of whole blood after hemorrhage in animals (Bond and Wright;<sup>106</sup> Mahoney<sup>107</sup>). These workers have noted a high incidence of reactions following the introduction of lyophile preparations into man. Earlier investigators had noted the occurrence of shock after the use of concentrated serums (Achard, Levy and Gallais<sup>108</sup>). It is apparent from these observations that blood plasma and serum constitute an acceptable form of blood substitute in conditions resulting from loss of whole blood, provided that sufficient hemoglobin remains in the blood stream to carry on oxygen transportation.

**Human Ascitic Fluid:** Human ascitic fluid as a blood substitute has been investigated both with animals (Davis and White<sup>40</sup>) and with man (Davis and Blalock<sup>109</sup>). The fluid is obtained from patients suffering from ascites due to cardiac failure or to portal cirrhosis of the liver, from whom it is frequently necessary to remove 12 to 15 liters of fluid every two to three weeks. The fluid is sterile and, if removed with aseptic precautions, can be stored in sterile flasks at temperatures of 0 to 5 C. for periods up to five months or longer. In our earlier work with this fluid no preservatives or anticoagulants were used. However, of late we have been adding sodium citrate (50 cc. of a sterile 5 per cent solution) to each 1,000 cc. of ascitic fluid. This prevents the formation of fibrin clots in the fluid and may obviate the possible occurrence of so-called "serum reactions." Recently we have established an "ascitic fluid bank" in the surgical research laboratory of this department, from which fluid can be withdrawn for use in the Charity Hospital. The fluid is submitted to several examinations, namely, the Kahn test, blood agar culture and quantitative determination of the protein and electrolyte content. In a series of specimens of ascitic

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105. Flosdorf, E. W., and Mudd, S.: Procedure and Apparatus for Preservation in "Lyophile" Form of Serum and Other Biological Substances, *J. Immunol.* **29**:389-425, 1935.

106. Bond, D. D., and Wright, D. G.: Treatment of Hemorrhage and Traumatic Shock by the Intravenous Use of Lyophile Serum, *Ann. Surg.* **107**:500-510, 1938.

107. Mahoney, E. B.: A Study of Experimental and Clinical Shock with Special Reference to Its Treatment by the Intravenous Injection of Preserved Plasma, *Ann. Surg.* **108**:178-193, 1938.

108. Achard, C.; Levy, J., and Gallais, F.: Recherches expérimentales sur quelques modifications colloïdales produites dans le sérum sanguin par l'injection de sérum concentré et par les saignées plasmatiques, *Compt. rend. Acad. d. sc.* **194**:1773-1777, 1932.

109. Davis, H. A., and Blalock, J. F.: Autologous and Homologous Transfusion of Human Ascitic Fluid, *J. Clin. Investigation* **18**:219-224, 1939.

fluid the total protein content was found to vary from 2 to 3.19 Gm. per hundred cubic centimeters; the albumin-globulin ratio from 1.1:1 to 2.3:1, and the sodium chloride content from 700 to 750 mg. per hundred cubic centimeters. As group-specific agglutinins are present in peritoneal transudates (Weil and Isch-Wall;<sup>110</sup> Yosida;<sup>111</sup> Schiff<sup>112</sup>), it is necessary to cross match the ascitic fluid with the blood of the prospective recipient. This is performed by mixing two drops of ascitic fluid with one drop of a suspension of red blood cells in isotonic saline solution on a slide which is allowed to stand for one hour before making a reading. The fluid, after removal from the refrigerator, should be placed in a bath of lukewarm water. Hot water should not be used, as coagulation of the proteins of the fluid at the circumference of the flask may occur, resulting in a post-transfusion reaction. Before use, the fluid should be filtered through fifteen layers of gauze. It should be administered by vein in the customary manner of transfusion.

It might be pertinent at this point to review briefly the results of ascitic fluid transfusion in animals suffering from hemorrhagic shock. Dogs weighing from 7 to 10 Kg. and anesthetized with pentobarbital sodium in appropriate amounts were used. Shock was considered to be present when sufficient blood had been removed to reduce the blood pressure to or below 60 mm. of mercury. The amount of blood removed varied from 3.4 to 5.2 per cent of the body weight. By transfusing human ascitic fluid it was possible to raise the blood pressure from the shock level and to maintain it at a normal level. The animals made a good recovery. There was no evidence of albuminuria, which suggests that the proteins of the ascitic fluid were retained by the animal. Illustrative data are shown (charts 4 and 5). It should be stated that preliminary cross-matching tests were carried out between the ascitic fluid and the blood of the prospective recipient.

The next step was to determine the availability of the fluid for human beings. At the time of writing, 22 transfusions with ascitic fluid have been performed, details of which will be given elsewhere. In a previous communication it has been shown that ascitic fluid is nontoxic and may be administered in large amounts intravenously (Davis and Blalock<sup>109</sup>). Despite the fact that ascitic fluid contains no hemoglobin, its use in states associated with acute loss of whole blood is rational, as in such states there is usually enough hemoglobin remaining to carry on the

110. Weil, P., and Isch-Wall, P.: H mo-agglutinines des divers liquides organiques, *Compt. rend. Soc. de biol.* **88**:173-175, 1923.

111. Yosida, K. I.: Ueber die gruppenspezifischen Unterschiede der Transsudate, Exsudate, Sekrete, Exkrete, Organextrakte und Organzellen des Menschen und ihre rechtsmedizinischen Anwendungen, *Ztschr. f. d. ges. exper. Med.* **63**:331-339, 1928.

112. Schiff, F.: Ueber die gruppenspezifischen Substanzen des menschlichen K rpers, Jena, Gustav Fischer, 1931, p. 71.

respiratory functions of the blood. Only 3 Gm. of hemoglobin per hundred cubic centimeters of blood is necessary to maintain adequate oxygenation in the mammalian organism.

A further step in this study was the concentration of ascitic fluid and its preservation in a lyophile form. Ascitic fluid was lyophilized

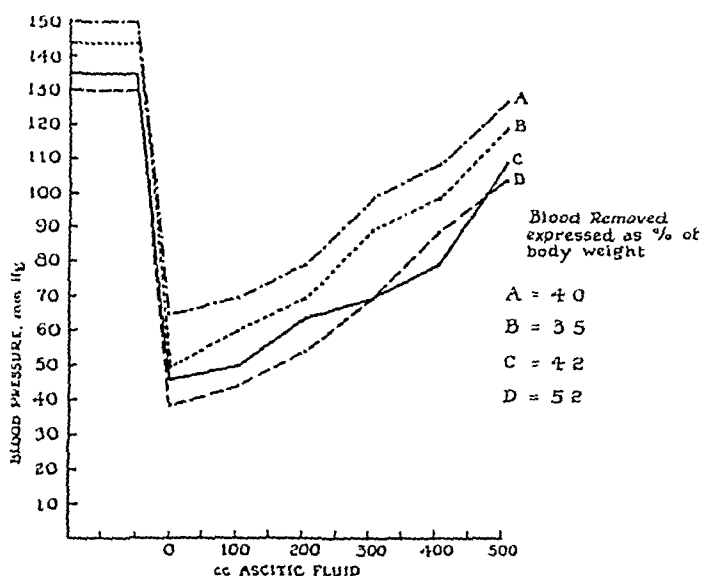


Chart 4.—Influence of ascitic fluid transfusion in cases of experimental hemorrhagic shock.

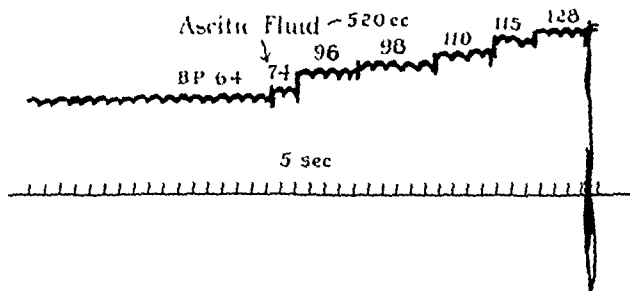


Chart 5.—Influence of ascitic fluid transfusion on the blood pressure in cases of experimental hemorrhagic shock.

according to the method of Flosdorf and Mudd.<sup>105</sup> This lyophile ascitic fluid was injected into dogs in which shock had been induced by graded hemorrhage. The blood pressure and the metabolic rate, which had fallen, were elevated to normal levels, where they were maintained (Mulder, Davis and Streeter<sup>113</sup>).

113. Mulder, A. G.; Davis, H. A., and Streeter, A.: On the Use of Dried (Lyophile) Ascitic Fluid in Hemorrhagic Shock, *Am. J. Physiol.* **126**:588-589, 1939.

## LOSS OF PLASMA

States associated with loss of plasma or plasma-like fluid from the blood stream present peculiar therapeutic problems and, therefore, merit separate consideration. In order to clarify this discussion, one may regard plasma as a mixture of proteins and water. Loss of either the protein or the aqueous fraction, or of both, may occur, and this loss may be acute or chronic. The different forms of plasma loss and their causes are given (table 2).

*Physiologic Effects of Loss of Plasma.*—The effects of loss of plasma are dependent on two facts: (1) the rate of loss and (2) the nature

TABLE 2.—Forms of Loss of Plasma

Rapidity of Loss	Fraction Lost	Etiologic Factors	
		Experimental	Clinical
Acute	Aqueous	Subcutaneous injection of hypertonic sodium chloride solution (Davis)	Acute dehydration due to excessive perspiration, vomiting or diarrhea
Chronic	Aqueous	Water deprivation	Chronic dehydration due to excessive loss or insufficient intake of water
Acute	Protein and Aqueous	1. Burns 2. Freezing 3. Intraperitoneal and subcutaneous injection of bile 4. Prolonged application of constrictor to extremity 5. Trauma 6. Manipulation of bowel 7. Tissue autolysis in vivo	Burns Bile peritonitis Freezing  Strangulation of bowel  Mesenteric obstruction Acute pancreatitis Trauma
Acute	Protein	Plasmapheresis	None
Chronic	Protein	Plasmapheresis Low protein diets	Nutritional edema Surgical hypoproteinemias

of the fraction lost. Acute loss of either the aqueous or the protein fraction or of both results in reduction of the plasma volume, increased concentration of the red blood cells and hemoglobin, reduction of the oxygen content of the blood and increase in the carbon dioxide content. Clinically, the evidences of secondary shock manifest themselves. Chronic loss of the plasma fractions does not usually lead to shock. Loss of the aqueous portion of the plasma has already been considered in the discussion of dehydration. Chronic depletion of the protein fraction leads to reduction of the osmotic pressure of the blood, resulting in a disturbance of water balance. Edema of the skin and of the viscera and serous transudates may appear. Reduction of the total blood volume and hemoconcentration are absent with this form of loss of plasma. Disturbances in the motility of the gastrointestinal tract have been observed in association with diminution of the protein frac-

tion of the plasma (Barden, Ravdin and Frazier <sup>114</sup>). Hypoproteinemia in surgical patients, which is usually due to a variety of factors, such as insufficient protein intake, infection, loss of protein by drainage, hemorrhage before or during operation and deficient protein synthesis (Jones and Eaton;<sup>115</sup> Curphey and Orr <sup>116</sup>), may also lead to delayed wound healing and even to wound disruption (Thompson, Ravdin and Frank <sup>117</sup>).

*Measurement of Degree of Plasma Loss.*—The extent and type of loss of plasma may be measured directly or indirectly. Direct determination of the plasma volume may be carried out by the various dye methods, of which Gregersen and Gibson's <sup>118</sup> is probably the most accurate. Indirect determinations will reveal hemoconcentration with

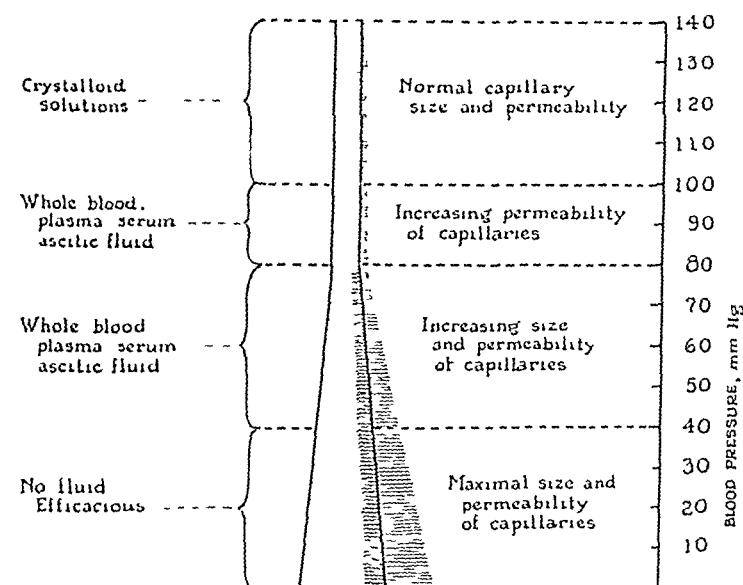


Chart 6.—Shock due to loss of plasma; efficacy of replacement fluids in relation to capillary permeability.

normal or slightly lower concentration of plasma protein when acute loss of the protein and aqueous fractions of the plasma has occurred.

114. Barden, R. P.; Ravdin, I. S., and Frazier, W. D.: Hypoproteinemia as a Factor in the Retardation of Gastric Emptying After Operations of the Billroth I and II Types, *Am. J. Roentgenol.* **38**:196-202, 1937.

115. Jones, C. M., and Eaton, F. B.: Postoperative Nutritional Edema, *Arch. Surg.* **27**:159-177 (July) 1933.

116. Curphey, W. C., and Orr, T. G.: Edema in Surgical Patients, *Surgery* **1**:589-594, 1937.

117. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, *Arch. Surg.* **36**:500-508 (March) 1938.

118. Gregersen, M. I., and Gibson, J. G.: Conditions Affecting Absorption Spectra of Vital Dyes in Plasma, *Am. J. Physiol.* **120**:494-513, 1937.

When the aqueous fraction alone has been lost, the hemoconcentration will be accompanied with an increased concentration of the plasma proteins. In the presence of chronic loss of the protein fraction the erythrocytes and hemoglobin are normal or diminished in amount, but the level of plasma protein, of course, is lowered.

*Fluid Replacement.*—Reduction of the plasma volume due to dehydration will not be reconsidered in the following discussion. In cases of acute loss of plasma with hemoconcentration and its sequelae, the crux of the therapeutic problem is the institution of fluid replacement before the capillary walls have been irreversibly damaged by oxygen lack (chart 6). Crystalloid solutions should be used with caution, are often ineffective and may actually reduce the plasma proteins still further by washing them out of the blood stream into the interstitial tissue spaces, the peritoneal cavity and the site of trauma (Beard and Blalock;<sup>54</sup> Davis<sup>55</sup>). Acacia solutions likewise are contraindicated, for two reasons: 1. Such solutions may interfere with the respiratory functions of the blood by coating the red blood cells. 2. They may adversely affect regeneration of plasma protein by the liver. The presence of hemoconcentration and increased viscosity of the blood would suggest that solutions of normal human proteins without red blood cells might prove more effective than whole blood. Such solutions are plasma, serum and human ascitic fluid. Although ascitic fluid has a somewhat lower protein content than either plasma or serum, it is usually available in larger quantities, and as much as 2,500 cc. may be given during twenty-four hours. If dehydration complicates the acute loss of plasma, crystalloid solutions may be given, but only after the plasma volume has been restored by protein-containing solutions. It is important to remember that the level of the blood pressure is no indication of the degree of loss of plasma. By the time the blood pressure has reached the accepted "shock" level (80 mm. of mercury), a considerable loss of plasma has occurred, and there are present a severe degree of oxygen lack and an increased permeability of the capillaries. A more reliable prognostic index is the level of hemoconcentration, but this, too, may be misleading if dehydration or loss of whole blood is superimposed on the loss of plasma. The most trustworthy criterion of circulatory deficiency associated with acute loss of plasma is the level of oxygen saturation of the blood. Determination of the potassium content of the blood as an index of the severity of shock has not proved reliable in our hands. The dangers connected with administration of crystalloid solution in the presence of conditions associated with reduction of the plasma volume are illustrated by the following 2 cases.

CASE 2.—A white girl aged 13 years was admitted to the Charity Hospital suffering from first and second degree burns of the left arm, right axilla, back and abdomen. Each day 2,000 to 3,000 cc. of 5 per cent dextrose in isotonic

saline solution was administered by vein. The blood pressure gradually fell, and the patient died five days after admission to the hospital. Autopsy revealed extreme edema of the subcutaneous tissues of the entire body, which, when incised, released large amounts of straw-colored fluid. The pleural cavities each contained 300 cc. of clear straw-colored fluid. The pericardial cavity contained an excess of fluid. The lungs were voluminous and frothy on section, and microscopic examination revealed pulmonary edema. Other observations were hemorrhage into the left adrenal gland, fatty metamorphosis of the liver and extreme distention of the mucosal capillaries of the gastrointestinal tract.

The water-logging of the tissues, the bilateral hydrothorax and the pulmonary edema probably hastened the circulatory failure in this patient. Trusler and his co-workers<sup>119</sup> stated the belief that water intoxication may follow the excessive administration of fluids to patients suffering from shock due to burns. The reduction of the total plasma volume will not be revealed by simple determination of the level of serum protein. If an effort is made to replace the plasma which has been lost by administering solutions containing proteins, preferably of human origin, the subsequent use of crystalloid solutions is less likely to be attended with untoward results. Case 3 confirms this statement.

CASE 3.—A white man aged 24 years was admitted to the Charity Hospital suffering from first and second degree burns of the face, neck, trunk and upper extremities, resulting from the explosion of a kerosene stove. The blood pressure was 120 systolic and 80 diastolic and remained stable. On the first day, 3,000 cc. of 10 per cent dextrose in isotonic saline solution was given by vein. On the second day, another 1,000 cc. of the same solution was administered. The condition of the patient was not good. The total amount of urine secreted in the first forty-eight hours was 500 cc. On the third day, because of the low output of urine, another 1,000 cc. of 10 per cent dextrose in isotonic saline solution was given by vein. The patient's face and body were now edematous. The value for serum proteins was 5.5 Gm., that for albumin 4.3 Gm. and that for globulin 1.2 Gm. per hundred cubic centimeters. The patient was seen by one of us (H. A. D.) on the evening of the third day, and an ascitic fluid transfusion was decided on. Accordingly, 475 cc. of group-compatible human ascitic fluid was given by the intravenous route at a rate of 5 cc. per minute. A brisk diuresis occurred during the transfusion. The following day the edema of the face and body had disappeared, and the output of urine was considerably increased. On the fifth day after admission, the level of serum protein had risen to 6.8 Gm. per hundred cubic centimeters. The patient made an excellent recovery, without recurrent edema of the face or of the body.

The therapeutic problem in cases of chronic loss of the protein fraction of the plasma is not prevention of secondary shock but correction of the disturbance of distribution of the body fluids resulting from lowering of the osmotic pressure of the blood. It is apparent that only protein-containing fluids, such as whole blood, plasma, serum and

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119. Trusler, H. M.; Egbert, H. L., and Williams, H. S.: Burn Shock: The Question of Water Intoxication as a Complicating Factor, *J. A. M. A.* **113**:2207-2213 (Dec. 16) 1939.



ascitic fluid, are indicated. It should be pointed out that in treating hypoproteinemia with ascitic fluid transfusions it is not necessary to limit the amount of fluid transfused to 500 cc. As much as 2,500 cc. of ascitic fluid may be transfused during a period of twenty-four hours. Lyophile plasma has been utilized in such hypoproteinemic states, but post-transfusion reactions have been severe (Thompson, Ravdin, Rhoads and Frank<sup>120</sup>). Acacia solutions are contraindicated because of their proved deleterious action on protein regeneration. Elman and Weiner<sup>121</sup> have recommended the use of intravenous fluids containing amino acid mixtures. Finally, the danger of intravenous hypertonic and even isotonic solutions of sodium chloride should be kept in mind when hypoproteinemia is present. Edema of the body tissues may be precipitated, due to fixation of the sodium chloride and water in the tissues. Such "salt" edemas are apt to resist treatment. The use of desoxycorticosterone acetate is contraindicated.

#### CONCLUSIONS AND SUMMARY

Fluid replacement in various surgical states associated with a reduction of the water, electrolyte, blood and plasma content of the body is considered. Such replacement must be based on an understanding of the underlying disturbances of body function. The experimental and clinical aspects of ascitic fluid transfusion are discussed.

NOTE.—Since this paper was submitted for publication, we have transfused into human beings ascitic fluid which preliminary cross-matching tests had revealed to be incompatible with the blood of the prospective recipient. No reactions occurred. This will be discussed in more detail in a forthcoming paper.<sup>122</sup>

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120. Thompson, W. D.; Ravdin, I. S.; Rhoads, J. E., and Frank, I. L.: Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, *Arch. Surg.* **36**:509-518 (March) 1938.

121. Elman, R., and Weiner, D. O.: Intravenous Alimentation with Special Reference to Protein (Amino Acid) Metabolism, *J. A. M. A.* **112**:796-802 (March 4) 1939.

122. Davis, H. A.: The Inactivation of Group-Specific Isoagglutinins in Relation to the Transfusion of Incompatible Plasma, Serum and Ascitic Fluid, to be published.

# IMPROVEMENT IN BLOOD TRANSFUSION SERVICE

## II. ESTABLISHMENT AND OPERATION OF A BLOOD TRANSFUSION SERVICE

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CINCINNATI

The selection and artificial preparation of high-titered test serums, the study of the cause and prevention of hemolytic transfusion reactions, the consideration of the role of subgroups and intragroup agglutinins in transfusion accidents, and the adoption of a simple, accurate technic for determination of blood grouping and compatibility have been described. All are parallel actions directed toward a single purpose, the transfusion of blood with the greatest simplicity and the least possible delay in laboratory procedure, with observance of the best known standards of safety.

Another major obstacle to the dispatch of blood transfusion service in large municipal hospitals is the inaccessibility of blood donors. There are delays, inefficiency and tragic results attendant to location of friends and relatives and the laboratory search for compatible and suitable bloods for patients whose bloods are of the rare groups. Occasionally, there is an emergency which does not permit even the time used to select a donor for a patient whose blood is of the common group. These are matters of ordinary knowledge to any resident physician. Any innovation in blood transfusion service which abolishes these delays results in a decreased morbidity and the saving of lives. It becomes another, parallel force designed to accomplish the same purpose as the technical improvements and considerations mentioned.

Such an innovation is the establishment of the American Red Cross Blood Transfusion Service at the Cincinnati General Hospital. This service consists of a blood bank and a volunteer donor bureau. In this paper will be presented the details of organization and method of operation of this service. A statistical analysis of the first 3,077 transfusions of refrigerated blood will follow.

### EARLY INVESTIGATION

Although a few experimental works were recorded earlier in this century, the widespread clinical use of preserved blood is strictly a

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development belonging to the past decade. Rous and Turner,<sup>1</sup> of the Rockefeller Institute, preserved blood by adding an anticoagulant medium consisting of two parts of isotonic sodium citrate solution and five parts of isotonic dextrose solution to three parts of whole blood. They were chiefly interested in red blood cells and noted that in this mixture the cells remained intact for four weeks. Their only attempts at transfusion were experimental and were limited to the transfusion into animals of red blood cells suspended in physiologic solution of sodium chloride, the plasma having been discarded. The first recorded transfusion of preserved whole blood was that of Weil.<sup>2</sup> Blood from three to five days old, to each 10 cc. of which 1 cc. of 10 per cent sodium citrate solution had been added, was transfused. During the World War Robertson<sup>3</sup> employed the Rous-Turner technic in 20 cases. The red cells of blood which had been stored for as long as twenty-four days were given intravenously after suspension in isotonic salt solution. The plasma was discarded because of fear of too high a concentration of sodium citrate in the whole blood mixture. Interest lagged in this investigation for a number of years after the World War, but it received considerable encouragement when Yudin,<sup>4</sup> of Moscow, Russia, reported the results in 1,000 transfusions of refrigerated cadaver blood. Added impetus also emanated from Russia as a result of reports of the transfusion of preserved blood obtained from the placental end of the severed umbilical cord. The transfusion of placental blood was first reported from this continent by Goodall.<sup>5</sup>

At the Cincinnati General Hospital, use of the cadaver as a source of blood was investigated only from the standpoints of obtaining the blood in sterile culture and of determining how much blood could be obtained. Before blood was drawn from the cadaver, the following requirements had to be met:

1. It was necessary to obtain an autopsy permit and to draw the blood within six hours after death, since the danger of penetration of intestinal bacteria into the blood stream after six hours is great.
2. It was necessary to predetermine that no infectious disease was present at the time of death.

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1. Rous, P., and Turner, J. R.: Preservation of Living Red Cells in Vitro, *J. Exper. Med.* **23**:219, 1916.

2. Weil, R.: Sodium Citrate in the Transfusion of Blood, *J. A. M. A.* **64**:425 (Jan. 30) 1915.

3. Robertson, O. H.: Transfusion with Preserved Red Blood Cells, *Brit. M. J.* **1**:691, 1918.

4. Yudin, S. S.: Transfusion of Stored Cadaver Blood: Practical Considerations; the First Thousand Cases, *Lancet* **2**:361, 1937.

5. Goodall, J. P.; Anderson, F. O.; Altimas, G. T., and McPhail, F. L.: Inexhaustible Source of Blood for Transfusion and Its Preservation, *Surg., Gynec. & Obst.* **66**:176, 1938.

3. Freedom from syphilis as determined by previous negative Wassermann or Kahn reactions was necessary.

Once these requirements were met it was found that only 1 cadaver each three or four weeks was available for extraction of blood. The average amount obtained from each of 3 cadavers by cannulating the internal jugular vein with the head in a dependent position was 1,200 cc. Efforts toward obtaining blood from this source were abandoned because the amount obtainable was too small to be of value to a transfusion service which required approximately 4,000 cc. of blood per day and also because it was believed that patients would not be willing to accept the transfusion of blood from a cadaver.

With the technic outlined by Goodall and in cooperation with the obstetric department, fetal cord blood as a source of supply was investigated. Quantities obtained in sterile culture amounted to about 115 cc. for each cord. The available cords for which negative Wassermann reactions could be obtained averaged six each day. Thus six operations and six sets of sterile equipment were required in order to obtain less than 700 cc. of blood. The pooling of these bloods in order to obtain amounts for practical use and the number of grouping tests required in the laboratory before they could be pooled were added difficulties. The experience in this clinic is that an equal amount of blood can be obtained with much less difficulty from friends and relatives and from other volunteer donors. For this reason, placental blood obtained from fetal cords is regarded here as an impractical source of supply.

The problem which confronts a large hospital with a busy transfusion service is not the source of the blood but rather the need for a reserve supply which will eliminate delay in cases of emergency and which can be depended on so that elective transfusions may be scheduled in advance for purposes of expediency. For this reason it is probably true that the outstanding contribution resulting from the transfusion of preserved cadaver and placental blood has been to make physicians connected with the blood transfusion services in large hospitals conscious of the fact that blood from ordinary donors can be drawn in advance and preserved and the supply replenished whenever the opportunity affords, with creation of a constant supply of blood which can be depended on to absorb delays incident to either emergency or elective transfusions.

As an outgrowth of this consciousness, blood banks are now operating in several hundred hospitals in the United States. The first one was established at the Cook County Hospital in Chicago in 1937.<sup>6</sup> Others are maintained at the University of Pennsylvania Hospital, the Phila-

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6. Fantus, B.: The Therapy of the Cook County Hospital: Blood Preservation Technic, *J. A. M. A.* **111**:317 (July 23) 1938.

delphia General Hospital, the Presbyterian Hospital, New York City, the New York Hospital, the Los Angeles County Hospital and the Cincinnati General Hospital.

#### PRESENT STATUS OF BANK BLOOD

Blood is a living fluid, and the limitations of its use when preserved have become a problem of major interest. In the short space of two years much work has been done in various clinics in order to answer the natural questions which arise pertaining to these limitations. The question of how long blood can be stored before use can be answered only by further study of the changes which occur in the many different components desirable in transfusions. When the stability of each of these components has been determined and is known in terms of days, the answer to the question of how long blood may be kept before transfusion will be known. The length of time will undoubtedly vary a great deal, depending on what component of the blood is desired for a particular transfusion. The only two methods of approach for this study are: (1) determination of the changes which occur in preserved blood and (2) evaluation of the results of transfusion of such blood.

In regard to the changes which occur in preserved blood, the following contributions are of interest. Using Kjeldahl nitrogen determinations on properly refrigerated blood as indexes of proteolysis, Kremerman<sup>7</sup> concluded that blood stored for twenty-one days is not toxic to the recipient as far as the degree of proteolysis is concerned. Scudder<sup>8</sup> observed a shift of potassium ions from cells to plasma and stated that care should be taken in using it in certain types of cases. It seems doubtful, however, that the amount of free potassium is sufficient to cause toxic symptoms.

The marked hemolysis of red cells which occurs at the end of ten days has been a subject of much discussion, since erythrocytes are the important elements in the treatment of hemorrhage and anemia. Following the lead offered by the early work of Rous and Turner, DeGowin<sup>9</sup> has shown that the addition of 13 parts of 5.4 per cent of dextrose solution and 2 parts of 3.2 per cent of sodium citrate solution to each 10 parts of blood prevents rapid hemolysis and delays diffusion of the potassium ion into the serum. It is obvious, however, that this mixture should not be added routinely to all bank blood, since the dilu-

7. Kremerman, R. B.: *Med. eksper.*, November 1938, p. 29.

8. Scudder, J.; Drew, C. R.; Corcoran, D. R., and Bull, D. C.: *Studies in Blood Preservation: I. Repartition of Potassium in Cells and Plasma*, *J. A. M. A.* **112**:2263 (June 3) 1939.

9. De Gowin, E. L.; Harris, J. E., and Plass, E. D.: *Changes in Blood Preserved for Transfusion*, *Proc. Soc. Exper. Biol. & Med.* **50**:126, 1939.

tion would reduce the blood efficiency of the fluid transfused to 40 per cent per unit volume. The result of DeGowin's work may find practical application in those cases in which the volume of fluid transfused can be raised to the point desired without contraindication. Certainly in the treatment of shock, in which the plasma is the desired element and the erythrocytes are generally considered inconsequential, any dilution of bank blood is undesirable, because of the diminution in the hydroscopic action of the plasma which results.

Rhoads and Panzer<sup>10</sup> stated the belief that bank blood is an unsatisfactory source of plasma prothrombin for treatment of the hemorrhagic diathesis associated with jaundice. They based their opinions on determination of the prothrombin time of bank blood plasma by the method of Quick.<sup>11</sup> Lord and Pastore<sup>12</sup> made the same study on bank blood, using the method of Warner, Brinkhous and Smith<sup>13</sup> as well as the method of Quick. They corroborated the work of Rhoads and Panzer by the method of Quick but showed that the prothrombin level dropped only to 84 per cent in eight days as compared with 23 per cent by the Quick test with the method of Warner, Brinkhous and Smith. At the end of twelve days the prothrombin time was 27 per cent by the method of Quick and 75 per cent by the method of Warner, Brinkhous and Smith. These data were on properly refrigerated blood (2 to 4 C.). Determinations made by Lord and Pastore on the prothrombin time of plasma kept at ordinary ice box temperature showed the prothrombin time to be only 48 per cent in twelve days (method of Warner, Brinkhous and Smith). The discrepancy in the results obtained with use of the method of Warner, Brinkhous and Smith as compared with those obtained by the method of Quick was partially explained by Lord and Pastore by the fact that the quick test controls only the calcium and thromboplastin (since Quick correctly considered it unimportant to control the fibrinogen content, which is normal in the blood of the jaundiced patient) and that the Warner, Brinkhous and Smith test controls the fibrinogen as well. Since the difference in the level in the prothrombin time of bank blood when determined by the two methods is created by the addition of fibrinogen and since the fibrinogen content of

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10. Rhoads, J. E., and Panzer, L. M.: The Prothrombin Time of "Bank Blood," *J. A. M. A.* **112**:309 (Jan. 28) 1939.

11. Quick, A. J.: The Nature of the Bleeding in Jaundice, *J. A. M. A.* **110**: 1658 (May 14) 1938.

12. Lord, J. W., and Pastore, J. B.: Prothrombin Content of Bank Blood, *J. A. M. A.* **112**:309 (Jan. 28) 1939.

13. Warner, E. D.; Brinkhouse, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, *Am. J. Physiol.* **114**:667, 1936.

bank blood plasma has been shown by Bancroft<sup>14</sup> to be normal quantitatively, a possible explanation of the difference in results may lie in the fact that there are qualitative changes in the fibrinogen of bank blood plasma. However this may be, Lord and Pastore concluded that bank blood is an adequate source of plasma prothrombin for about nine days, as determined by the accurate method of Warner, Brinkhous and Smith. They also concluded that carefully controlled refrigeration is an important factor in the preservation of prothrombin. Their conclusions are reasonable, and, since the fibrinogen content of the plasma in jaundiced patients is quite normal, the prothrombin which is transfused should be affected by the fibrinogen of the patient in such a manner as to decrease the clotting time, just as occurs when the fibrinogen is added in a test tube according to the method of Warner, Brinkhous and Smith. A carefully controlled study of the effects of bank blood of various ages on the prothrombin time of patients with jaundice has never been made and would be of extreme value at present in order to determine this particular limitation of bank blood.

Another question of interest as to the limitations of bank blood is that of sterility. Reports showing the results of culture of specimens taken from bank blood are too numerous to mention. It is generally agreed that, provided careful technic is exercised in the drawing of the blood in a closed system, it is not desirable routinely to culture bank blood before it is transfused. The mere taking of the sample for culture subjects the specimen to increased opportunity for contamination. Novak<sup>15</sup> concluded that pyrogens produced by bacteria growing in bank blood may be a cause of transfusion reactions and stated that the frequency of transfusion reactions with bank blood "ranges up to 50 per cent depending on the index used for defining a transfusion reaction." He did not say where these statistics were obtained. Assuming that the lack of sterility is a major cause of transfusion reactions, Novak advocated the addition of sulfanilamide, 20 mg. per hundred cubic centimeters of blood, as a bacteriostatic agent. His method was to inoculate 10 cc. of fresh blood with twenty-four hour cultures of *Staphylococcus albus*, *Pseudomonas aeruginosa* and hemolytic spore-forming rods. The specimens were then plated on agar, and the colonies were counted after refrigeration for forty-eight hours at 4 to 6 C. Complete bacteriostasis and in some cases sterilization were effected by a concentration of sulfanilamide of 20 mg. per hundred cubic centimeters. It is doubtful that pyrogens produced by bacteria growing in bank blood drawn with proper sterile technic are a cause of transfusion reactions, since the

14. Bancroft, F. W.; Stanley-Brown, J., and Quick, A. J.: Post Operative Thrombosis and Embolism, *Am. J. Surg.* 28:648-668, 1935.

15. Novak, M.: Preservation of Stored Blood with Sulfanilamide, *J. A. M. A.* 113:2227 (Dec. 16) 1939.

incidence of reactions in some reported series of bank blood transfusions is no greater than the incidence of reactions in reported series of transfusions of fresh blood.

Drew and Scudder<sup>16</sup> carefully determined the fate of thrombocytes in bank blood and found that they rapidly fall to less than 100,000 for each cubic millimeter in twenty-four hours and to 40,000 at the end of three days. Kolmer<sup>17</sup> also demonstrated the instability of platelets. Because of this, bank blood should not be used as a source of thrombocytes.

Numerous workers<sup>18</sup> have demonstrated the degree of spontaneous hemolysis in properly refrigerated bank blood. The results of their studies indicate that preserved blood is a good source of erythrocytes up to five days and should not be used for this purpose after eight days.

The age limitation that should be placed on preserved blood which is used in the treatment of infections, septic states and septicemias is not yet clear and must necessarily depend on the component or components of blood desired in a particular case. The supportive value of the elements contained in plasma for nutrition and of the red cells in combating the anemia associated with these conditions is well known. Since the value of immune substances, both specific (antibodies) and nonspecific bactericidal (leukins and plakins), even in fresh blood in 200 to 500 cc. amounts is debatable, deterioration of these substances in preserved blood as shown by Kolmer<sup>17</sup> may or may not be a limitation to its use. Observations made during his studies on citrated blood preserved at 4 to 6 C. were as follows:

1. Complement is well preserved up to fourteen days.
2. Bactericidal activity for *Staphylococcus aureus*, the beta hemolytic streptococcus and *Bacillus coli* is decreased after seven days' preservation.
3. The phagocytic activity of neutrophils on the same three organisms is definitely reduced within seventy-two hours, becoming markedly so about the fifth day owing to degenerative changes in the leukocytes.
4. The leukocytes display degenerative changes within twenty-four hours.
5. The platelets exhibit distinct clumping immediately, with evidence of deterioration in twenty-four hours. They are scarce at the end of forty-eight hours.

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16. Drew, C. R.; Edsall, K., and Scudder, J.: *Studies in Blood Preservation*, J. Lab. & Clin. Med. **25**:240, 1939.

17. Kolmer, J. A.: *Preserved Citrated Blood "Banks" in Relation to Transfusion in Treatment of Disease with Special Reference to Immunologic Aspects*, Am. J. M. Sc. **197**:442, 1939.

18. de Gowin, Harris and Plass.<sup>9</sup> Drew, Edsall and Scudder.<sup>16</sup> Kolmer.<sup>17</sup>



Although it is not established, Kolmer has stated the belief, as have many others, that immune substances in transfused blood are efficacious in the treatment of septic conditions and has concluded that fresh blood is preferable and that preserved blood more than 2 to 3 days old should not be used for these purposes.

The second method of approach to the study of the value of preserved blood, namely, the study of results of transfusion of such blood, is one which deserves careful attention and will increase in value as carefully compiled statistics accumulate. It is from this standpoint that the statistical analysis of 3,077 transfusions of refrigerated blood at the Cincinnati General Hospital becomes of interest. The results of this study are commented on as it is presented.

Schaefer and Wiener<sup>19</sup> traced the fate of the erythrocytes of bank blood after transfusion and found that the result when five to eight day

*Age of Blood for Various Conditions*

Condition of the Patient	Age of Blood in Days *
Shock not associated with toxemia (hemorrhagic, traumatic, surgical, thermal) .....	21
Anemia not associated with sepsis. . . . .	8
Hypoproteinemia .....	21
Infection, septic state, septicemia.....	3
Hemorrhagic diathesis in obstructive jaundice...	8
Thrombopenic purpura . . . . .	1½ (12 hrs.)

\* The age limitations expressed above are maximum, and in actual practice almost all units of blood are issued several days before these time limits expire.

old blood was used was about the same as when fresh blood was transfused. The period of survival of the erythrocytes was from three to four months. However, four specimens of ten to twenty day old blood were transfused, and the erythrocytes given could not be demonstrated in the circulation of the recipient after from one to three weeks.

In the operation of the blood bank at the Cincinnati General Hospital it has been ordinary practice to dispense units of blood with regard to the known limitations of preserved blood for the particular cases, the age of the blood issued depending on the diagnosis submitted for the patient. Although it is constantly subject to change as more is learned concerning these limitations, a guide to the members of the house staff is posted at the time of this writing (see accompanying table). Experience of sixteen months' duration, during which time more than 3,500 transfusions of preserved blood have been given, has shown that these time limitations have not interfered with the practical operation of the blood bank service.

19. Schaefer, G., and Wiener, A. S. Limitations in the Use of Preserved Blood for Transfusions, *Quart. Bull., Sea View Hosp.* 5:17, 1939.

## ORGANIZATION OF THE SERVICE

The American Red Cross Blood Transfusion Service, consisting of a blood bank and a volunteer donor bureau with headquarters at the Cincinnati General Hospital, is the first of its kind. It is without precedent that a local chapter of the American Red Cross has collaborated with a municipal hospital in order to produce such an organization. The Cincinnati and Hamilton County Chapter of the American Red Cross first became interested in a service to be offered all hospitals and physicians in Hamilton County early in 1938. In May 1938 the officials of the Red Cross, in order to ascertain whether such a service was badly needed, met with a group consisting of physicians, superintendents of Cincinnati Hospitals, members of the Hamilton County Board of Health and representatives of industrial hospitals. A plan of operation was proposed at this time and was given unqualified approval by all members of this group. On the basis of this assurance, the Red Cross was willing to proceed with the financial support of the plan as outlined. The American Red Cross Blood Transfusion Service, with headquarters at the Cincinnati General Hospital, was then organized and has now been in full operation for more than a year. The administration, the headquarters, the physical equipment, the duties of the personnel and the method of operation of the service in relation to hospitals and physicians of Hamilton County are described in the following sections.

## ADMINISTRATION OF THE SERVICE

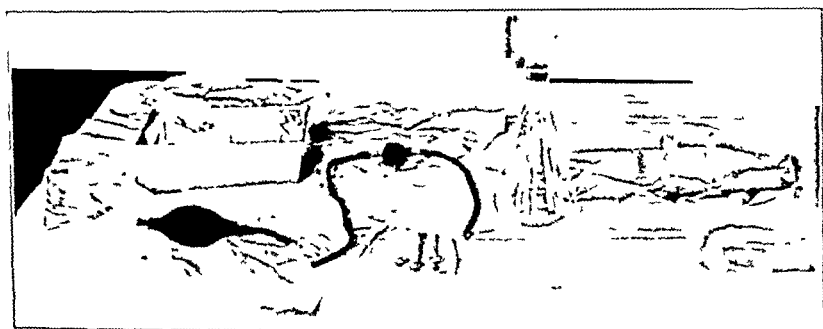
The service is known as the American Red Cross Blood Transfusion Service. The medical direction and administration are responsibilities of a service committee appointed by the Cincinnati and Hamilton County Chapter of the American Red Cross, subject to the approval of the directing medical staff of the Cincinnati General Hospital. The interests of hospitals other than the Cincinnati General are represented by two memberships on this committee. There are a director and an assistant director of the service from the department of surgery at the Cincinnati General Hospital and the University of Cincinnati, who are also members of the service committee. This committee meets periodically to determine the policies of the service. The director or the assistant director is constantly available for normal operation.

## HEADQUARTERS AND EQUIPMENT

The Cincinnati General Hospital provides space which measures 48 by 15 feet (14.6 by 4.5 meters) for the office, two booths for the drawing of blood and a laboratory and blood storage room. The hospital also furnishes water, janitor and laundry service, steam sterilization and electricity for lights, refrigeration and ventilation. Mechanical, carpentry and repair service are also partially maintained by the hospital. Items

of operating equipment, such as gauze sponges, cotton, towels, sheets, wrappers, rubber gloves, sterilizing solutions, hydrogen peroxide, iodine, procaine hydrochloride, sodium citrate, collodion, applicator sticks, cresol, ether, acetone and distilled water, are supplied at the expense of the hospital.

The Red Cross assumed the cost of physical changes in the space, including partitions, decorating, electrical wiring, light fixtures and plumbing. They also provided all fixed equipment for the office, booths and laboratory, and they supply all operating equipment not mentioned. The office equipment includes desks, chairs, filing and storage cabinets, one typewriter, office supplies and printed forms. Each booth is equipped with a donor bed, two utility tables and auxiliary lights. The laboratory equipment, purchased and supplied by the Red Cross, includes one refrigerator, the laboratory desk and sink, storage cabinets for linen and sterile supplies, one microscope, one drying oven, human blood grouping



Items included in the donor set.

serums, glass slides, Petri dishes, glass pipets and platinum wire. The Red Cross also furnishes the items used in the donor sets with the exception of the muslin wrappers, gauze and powder paper. These items are as follows: One 28 by 28 inch (71 by 71 cm.) wrapper, one aluminum container, one 24 by 24 inch (61 by 61 cm.) wrapper, one 14 by 14 inch (35.5 by 35.5 cm.) wrapper, two test tubes stoppered with cotton, one hypodermic syringe, two gauze flask covers with powder paper folded inside, one gauze pad with 13, 15 and 25 gage needles with stilettes inserted, one 750 cc. graduated Erlenmeyer flask, one two-holed rubber stopper with glass bends and rubber tubing attached and one metal adaptor (see accompanying illustration).

#### PERSONNEL

The salaried personnel of the service consists of three laboratory technicians and a secretary. Their salaries are paid by the Red Cross. The technicians operate in three eight hour shifts, covering the entire

twenty-four hours of each day. Each is relieved for one day each week by a senior medical student provided by the National Youth Administration.

#### METHOD OF OPERATION

Early in the conception of this service it was considered highly desirable to incorporate into the service headquarters all the activities possible pertaining to the transfusion of blood. Reactions which result from the transfusion of blood are known to be caused by a multiplicity of factors, which may be due either to improper technic used in the drawing of blood or to careless handling and cleansing of the equipment which comes into contact with the blood, as well as to errors made in the laboratory testing of blood prior to transfusion. All these activities are carried out at central headquarters in order to avoid deviations from acceptable standards of technic, which would be uncontrollable if facilities were scattered and responsibility divided. Also, under a system of centralized control special problems relative to the known limitations of bank blood can best be met, and improvements in technic pertaining to any of the aforementioned procedures can be readily adopted and enforced. Too much emphasis cannot be placed on these considerations. A properly regulated blood bank should result in a decreased incidence of transfusion reactions, and it must consist of more than a refrigerator in which to store blood.

The blood transfusion service consists of two almost independent divisions, a blood bank and a volunteer donor bureau, operating under the same direction from the service headquarters. The operation of these divisions will be described separately.

1. *The Blood Bank.*—The house physician desiring blood for transfusion presents a small sample of defibrinated whole blood from the patient to the office, together with a request form bearing the date, the name of the physician, the service, the ward, the patient's name, the case number, the race of the patient, the diagnosis and the time the blood is desired. If for some reason relatively fresh blood is indicated, the maximum age possible is recorded on the request form. The technician, after determining the group of the blood sample, makes a direct match with a sample carried on the side of a unit (500 cc.) of blood of the same group from the refrigerator. If blood of the identical group is not available, group O bank blood is matched against samples of group A or B, and group A or B bank blood is matched against samples of group AB. The entire laboratory procedure requires twenty minutes, and in cases of extreme emergency the blood is issued in five minutes, pending the result of the direct match. This result is then relayed by telephone, which allows the physician to utilize the fifteen minutes required for the direct match in dispensing with all preparations preliminary to the

actual transfusion. To a tag form which is carried on the bottle of refrigerated blood issued is added the name of the patient, and this is filed alphabetically, according to his name. This file then becomes of value in determining the number of transfusions given to any patient and the identity of the donors.

For each withdrawal of 500 cc. of blood the secretary enters the data contained on the request form, the age of the blood issued and one debit unit in the monthly record of transactions. Each hospital service, such as medicine, general surgery, gynecology or obstetrics, is held responsible for a balance of its own debit and credit columns on this record. On the day following the transfusion the secretary makes a follow-up call to the responsible physician and records the presence or absence of a transfusion reaction. The total information compiled on the monthly record then becomes of value in the compilation of statistics for future study.

The replacement of a unit of blood which has been withdrawn becomes the obligation of the hospital service to which it was issued. In this way an obligation is not canceled when a physician who makes a withdrawal is transferred to another service or terminates his residency. Actual operation for more than a year has proved two important facts: first, that friends and relatives of patients and convalescent patients in whose cases there is no medical contraindication afford a more than adequate source of blood replacement and, second, that the bank will absorb without embarrassment reasonable delay, such as two to three days, in replacing a unit.

The physician presenting himself with a donor for replacement is expected to qualify the donor with a cursory medical history and physical examination. An accessible arm vein is required, because cutting down on a vein is not permitted. If these conditions are satisfied, the arm of the donor is draped and prepared for venipuncture by the technician while the physician scrubs. Preliminary grouping is not made unless there is an overstock or a shortage of one of the blood groups. The technician then assists the physician outside the sterile field in such matters as providing procaine hydrochloride, supplying sodium citrate for the flask, operation of the tourniquet, suction to the collecting system and collection of test tube samples of blood for future Kahn, grouping and matching tests.

The physician then assembles the donor set, injects 2 per cent procaine hydrochloride into the skin over the vein and, with the aid of the technician, adds 50 cc. of 2.5 per cent sodium citrate solution to the flask by suction through the collecting system. A 2.5 per cent sodium citrate solution is used in preference to a higher concentration in smaller volume in order to obtain better distribution of the solution throughout

the blood. Venipuncture is then made. The resulting per cent of sodium citrate (0.22) in the total volume (550 cc.) has proved to be sufficient to prevent any coagulation if the flask is almost constantly agitated by gentle rotation in alternate directions.

After 500 cc. of blood has been obtained, the rubber stopper and the contained glass bends are lifted from the flask before the venipuncture needle is withdrawn, and samples for Kahn tests and for grouping and matching are collected in the test tubes. The sterile cover, which consists of a powder paper and two layers of close-meshed muslin gauze filled with a layer of cotton sheet wadding, is then tied firmly over the neck and sides of the flask with gauze bandage.

At the end of the operation, entry is made in the credit column of the monthly record of transactions for the proper hospital service. The name of the donor is entered on the tag form which is attached to the flask's neck and on a form entitled "Donor of Bank Blood." The latter form is filed alphabetically according to the name of the donor and may be used in conjunction with the tag form in recalling him for a future transfusion in a case of protracted need. The test tube sample for future grouping and matching tests is labeled and placed in the metal container attached to the side of the flask. The sample for the Kahn test is labeled and placed with others for determination on the following morning.

The unit of blood is then placed on the "unclassified" shelf of the refrigerator and is removed to the "classified" shelf for the corresponding blood group after the blood group has been determined and a negative Kahn reaction has been obtained. In the event that the reaction is positive, a corroboratory Wassermann test is made. If the reactions to both tests are positive, the credit is withdrawn by drawing a red ink line through the entry on the monthly record. The physician is then notified of the cancelation, and a form letter is sent to the donor advising him of the need for treatment.

Once each month the names and addresses of all persons to whom this letter has been sent are submitted to the social hygiene council of the Public Health Federation for follow-up proceedings. During the past year over 300 persons having syphilis with no previous knowledge of the disease have been apprehended and directed to clinics or physicians for treatment. The value of this program as a collateral advantage to the community in the operation of the blood bank is obvious.

In addition to the performance of laboratory tests and assistance to the physician in drawing blood, the technicians are required to maintain proper equipment and tidiness in the donor booths, to make entries on printed forms in the absence of the secretary and mechanically to cleanse,

assemble and wrap donor sets preparatory to steam sterilization. Rigid adherence to the following procedure for preparation of items contained in the donor sets is maintained:

#### 1. Flask

- (a) Scrub with a brush and tap water. Use 2 ounces (60 cc.) of hydrogen peroxide if necessary. (No other chemicals and no soaps are to be used.) Brushes used are never to touch soap or be used for any other purpose.
- (b) Irrigate with tap water over an inverted hydrant for three minutes by the clock.
- (c) Inspect closely for visible contaminants. Repeat *b* if contaminants are present. *Avoid handling the mouth of the flask from this step on.*
- (d) Rinse the inside of the flask thoroughly with 270 cc. of distilled water and invert the flask in the drying oven.

#### 2. Rubber Tubing

- (a) All new rubber tubing introduced into a set must be boiled for fifteen minutes in 5 per cent sodium hydroxide solution.
- (b) Attach the tubes to a mechanical irrigator for five minutes. Repeat if visible contaminants are present.
- (c) Boil for fifteen minutes in 0.1 per cent sodium hydroxide solution.
- (d) Irrigate with tap water for two minutes.
- (e) Boil for five minutes in distilled water.
- (f) Shake well and place on the top shelf in the oven to dry.

#### 3. Rubber Stoppers

- (a) All new stoppers introduced into sets must be boiled for fifteen minutes in 5 per cent sodium hydroxide solution.
- (b) Rinse thoroughly in tap water.
- (c) Same as 2 *c*.
- (d) Same as 2 *d*.
- (e) Boil for five minutes in distilled water, connect to right-angled glass tubes and place in oven to dry.

#### 4. Glass Tubing

- (a) Attach to a mechanical irrigator for five minutes immediately after use.
- (b) Hold up to the light and inspect carefully for visible contaminants. Repeat step *a* and irrigate with hydrogen peroxide if contaminants are present.
- (c) Boil in distilled water for five minutes, and lay on a clean towel to dry.

### 5. Needles and Metal Adaptors

- (a) Scrub with hydrogen peroxide.
- (b) Irrigate with tap water.
- (c) Repeat *b* if contaminants are present.
- (d) Irrigate with distilled water.
- (e) Irrigate with 2 cc. of ether.

The laundering, steam sterilization and Kahn and Wassermann tests are the only operations performed outside the central quarters.

It is the duty of the technician to report any violation of sterile technic made in the drawing of blood to the director or assistant director of the service. The blood unit concerned is discarded, and the credit is withdrawn if a sterile culture is not obtained.

Each day an inventory of the units of blood of each group in the bank is recorded and filed. This information is of value in determining and anticipating an overstock or a shortage of any particular blood group in the bank. If an imbalance occurs, selective instead of random drawing of blood is exercised until it is corrected. This is done by determining the blood group of each prospective donor before drawing blood, rejecting donors of the group in which there is an overstock and selecting those of the group in which there is a shortage. Fortunately the volume of transfusions given by the service, an average of eight each day, is large enough to permit efficient operation most of the time without resort to selective drawing. It is our opinion that a blood bank would not be practicable for a hospital averaging less than five transfusions each day. To maintain an inventory of 50 units of blood, which is the least possible in order to secure a supply of the rarer blood groups, the average age of blood issued in a service requiring five transfusions a day would be ten days. The fluctuations in the supply resulting from ordinary delays in replacement in a service doing less in volume of transactions would result in periods of shortage of the rarer groups and overstocking with the commoner groups or vice versa. An overstock would require the waste of many bloods owing to age.

Because it is necessary to open the flasks in order to obtain specimens, which increases the opportunities for contamination, no effort is made to test units of bank blood for sterility.

The blood in the bank is maintained constantly at a temperature of from 2 to 4 C. Fluctuations in the temperature of the air inside the refrigerator caused by the necessary opening and closing of the doors is never more than 2 degrees (C.), as shown on recording thermometer charts.

Recordings of the temperature of the blood itself show no variation under the same conditions.



Separation of the blood from white and that from Negro donors in the bank has been a constant practice for reasons other than scientific ones. As is true in other phases of the practice of medicine, society is not yet willing to accept what medicine already knows. As far as is known, no immediate or ultimate undesirable effects accompany the transfusion of blood from a person with skin of one color to a person with skin of another.

2. *The Volunteer Donor Bureau.*—The volunteer donor bureau operates for the benefit of all hospitals in Hamilton County, not only the Cincinnati General Hospital. Early in the organization of the blood transfusion service it became obvious that major difficulties would be encountered if an attempt were made to extend the operation of blood banks to other hospitals. A unit of bank blood, if sent to a hospital at some distance away, must necessarily be replaced. This might be done by one of two methods. Either the replacement unit could be drawn at the hospital to which the unit was sent and returned by messenger to the bank, or the volunteer donor for replacement could be sent to the headquarters for the blood to be drawn there. The first method of replacement is highly undesirable, since it is impossible to control the technic under which blood is drawn unless it is done at central headquarters. The objection to the second method of replacement is that the service does not maintain a resident physician to draw blood. The only method of doing this would be to exploit the resident house staff at the Cincinnati General Hospital. Another objection to extension of the blood bank service to other hospitals is that the service is not anxious to usurp the functions properly belonging to a hospital relative either to the normally operating hospital procedure prior to transfusion or to the actual transfusion of blood. Instead, it desires to supplement these functions with a service which will make compatible and suitable blood quickly available whenever needed.

It is the experience of any hospital that in the majority of instances in which blood transfusion is desired the proper donor may be found among friends and relatives of the patient without undue delay. The volunteer donor bureau was organized as a second division of the Red Cross Blood Transfusion Service to serve all hospitals in Hamilton County when friends or relatives of the patient cannot be located or are not of the compatible blood group or when an emergency exists which does not permit waiting for laboratory search.

For this purpose the service maintains a list of certified blood donors which is available by telephone call day or night. The membership of this list was originally acquired through newspaper publicity. Its members are given a thorough physical examination. In addition, they are qualified each six months from the standpoints of age, good general health, negative Kahn reaction, absence of primary or secondary lesions of

syphilis, accessible arm veins and normal hemoglobin content of the blood. Periodic examinations are performed by volunteer physicians from the resident staff of the Cincinnati General Hospital. Each donor has expressed his willingness to respond at once to a service call, whether it be for an indigent patient or for one who is able to pay for the blood.

Each member of the list, when properly qualified, is issued a blood donor's identification book, which is his certificate of registration with the service. This book contains the signature of the donor, the date of registration and the registration number. In addition it contains a description of the donor, his blood classification, a record of the transfusions given through the service and a record of his periodic physical and laboratory examinations. The service maintains a card index in which each donor is classified according to blood group and the district in which he lives. The front of the card contains information necessary for quick communication with the donor. On the back of the card is a duplicate record of the results of periodic laboratory and physical examinations and of the transfusions given through the service.

With the permission of the Academy of Medicine of Cincinnati, each of its members and resident physicians of all hospitals in Cincinnati were acquainted with the operation of the service by means of a descriptive pamphlet. By telephone at any time, day or night, the physician may secure within an hour a volunteer donor of any blood group. The secretary or technician, on receiving the call, enters the necessary information on a printed form. The card index file of certified donors is then consulted, and a donor is selected with consideration for the following points: As far as possible the donors are used in rotation, in order that no one be asked to serve oftener than once each six weeks or to exceed four times each year and also that each donor is used often enough so that he retains his interest in the service. If the blood is needed for emergency use, a donor is called who lives close to the hospital. If the transfusion can be scheduled to meet the convenience of the donor, he is selected from an outlying district. Since all donor services are classified as to a "full pay," "part pay" or "indigent patient," an attempt is made also to distribute the "pay transfusions" throughout the list. Once the donor is selected, he is notified, and his name and the time of notification are recorded. A follow-up call to the physician from whom the request was received is made by the secretary on the next day. At this time the transfusion is credited to the donor on the back of his card in the index file.

Experience shows that to maintain a satisfactory list of donors it is necessary to give them every consideration to which they are entitled. For this reason the hospital staffs have been charged that the donor should be courteously received when he arrives at the hospital, that the blood should be drawn as promptly as possible and that he should be

dismissed with an expression of appreciation by the attending physician or nurse. They have also been asked not to call for a donor unless it is reasonably certain that he is to be used. After each transfusion the donor receives a letter of appreciation from headquarters.

When a call is received for a donor the person making the call is asked if the patient is indigent, "full pay" or "part pay." If the patient is indigent, no bill is sent. If he is classified as "full pay," the blood transfusion service sends a bill at the rate of \$50 per 500 cc. of blood. A "part pay" patient is one who is able to pay something for the blood given but cannot afford to pay the full rate. In this case the amount of the payment is to be determined by the patient or his relatives. All statements are sent to the accounting department of the hospital for submission to the patient. It is understood that the hospital is not responsible for collection of the money, its only function being submission of the bill. The hospital, however, is responsible for the payment of transportation of a donor to an indigent patient. Payment for all blood given is made by the patient to the service headquarters, and the sum is distributed at the rate of 80 per cent to the donor and 20 per cent to the service. Entry of financial details is then made.

Several reasons why the blood bank service could not be extended to hospitals other than the Cincinnati General Hospital have been stated. These objections would arise only if the sending of units of banked blood in response to requests for blood transfusion service were indiscriminate. If, however, in any instance of emergency the circumstances are such that the volunteer donor list service is not entirely adequate, bank blood is sent by taxicab. Such conditions are encountered only very occasionally, and the responsibility for replacement of these units in the bank is one that is readily and willingly met by the members of the resident staff of the Cincinnati General Hospital.

# IMPROVEMENT IN BLOOD TRANSFUSION SERVICE

## III. RESULTS OF 3,077 TRANSFUSIONS OF BANK BLOOD; A STATISTICAL ANALYSIS

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AND

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An important method of approach to the study of the value of preserved blood is an analysis of the results of transfusion of such blood. Just as some questions which arise as to the limitations of bank blood are answered by inquiry into the changes which occur in various components of blood when preserved, other, equally important questions, such as the effect of age of blood on the incidence and type of transfusion reactions, can be answered only by accurate recording of the results obtained from a long series of transfusions of bank blood. It is from this standpoint primarily that a statistical analysis of 3,077 consecutive transfusions of bank blood at the Cincinnati General Hospital becomes of interest. Numerous collateral points of interest which pertain to the practical operation of the service are also revealed by this study. These are of value to any one planning a similar organization and are commented on as they are presented.

A detailed description of the administration, headquarters and equipment and method of operation of the blood transfusion service, presented earlier, foretells the method by which the data were accumulated. The statistics presented were obtained from accurate records compiled at the time of transaction, from follow-up calls and from careful laboratory and case analyses when indicated.

### DATA

TABLE 1.—*Donors to Blood Bank (Jan. 1, 1939, to Feb. 23, 1940)*

Group	White (64.2%)		Negro (35.8%)		Both Races	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
AB	52	2.3	47	3.8	99	2.9
A	925	41.3	368	29.5	1,293	37.1
B	184	8.2	262	21.0	446	12.8
O.....	1,079	48.2	570	45.7	1,649	47.2
Total ..	2,240	100.0	1,247	100.0	3,487	100.0

From the Department of Surgery of the University of Cincinnati College of Medicine and the Cincinnati General Hospital.

## COMMENT

Of 3,487 donors who gave blood to the bank in the period from Jan. 1, 1939, to Feb. 23, 1940, 64.2 per cent were white and 35.8 per cent were Negroes. The percentage of occurrence of each of the four blood groups among the donors is given. A higher incidence of groups AB and B and a lower incidence of group A were present among the Negro donors. This concurs with numerous anthropologic observations.<sup>1</sup>

TABLE 2.—*Incidence of Syphilis Among Donors*

		Number of Donors	Positive Kahn Reactions	
			Number	Per Cent
White		2,240	58	2.6
Negro	.....	1,247	203	16.2
Total		3,487	261	7.5

## COMMENT

All prospective donors giving a history of syphilis were rejected. Despite this practice, 7.5 per cent of the blood drawn could not be used for transfusion because of positive Kahn reactions. In the white donor series the incidence of positive reactions for syphilis was 2.6 per cent as compared with 16.2 per cent for the group of Negro donors.

The loss due to syphilis could be eliminated by making tests before drawing blood for transfusion. However, if these tests were made through regularly scheduled morning laboratory procedure, prospective donors would have to return on the following day. Experience before the advent of the blood bank shows that many fail to return. If rapid tests were made preliminary to each drawing, additional expense for technical assistance would be necessary.

TABLE 3.—*Number of Donors Used and Transfusions Given*

	Number	Per Cent
Donors ...	3,487	100.0
Transfusions	3,077	88.2
Units discarded	410	11.8
Owing to Syphilis	261	7.53
Age .	95	2.72
Clotting	51	1.46
Breakage	3	0.09
	410	11.80

1. Wiener, A. S.: *Blood Groups and Blood Transfusion*, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

## COMMENT

Of the 3,487 units of blood drawn, 3,077, or 88.2 per cent, were given in transfusion. Four hundred and ten units and half-units were discarded; in all but 149 instances this was due to positive reactions for syphilis. Ninety-five units and half-units were lost because the time limit of twenty-one days had expired before they could be used. Most of this loss occurred during the early operation of the bank and was the result of accumulation of half-units not desired and of the rarer groups AB and B when encountered in families of donors. Anticipation of overstocking of this kind improved as operation of the bank progressed, and this loss was reduced in the later months of operation by determining the group when necessary before drawing blood. The waste of the remaining 54 units resulted from clotting because of insufficient agitation or difficulty with veins during the drawing and from breakage. There was no loss due to bacterial contamination. Much of the blood discarded became useful in various experimental laboratories.<sup>2</sup>

TABLE 4.—*Transfusions Given According to Hospital Service*

Service	Number	Per Cent
Surgery.....	1,265	41.11
Medicine.....	589	19.14
Gynecology.....	435	14.13
Pediatrics.....	227	7.37
Urology.....	150	4.87
Obstetrics.....	131	4.25
Contagious diseases.....	94	3.05
Dermatology.....	86	2.79
Otolaryngology.....	62	2.01
Orthopedics.....	24	0.78
Ophthalmology.....	7	0.22
Psychiatry.....	7	0.22
Total.....	3,077	100.00

## COMMENT

The amount of blood given in each hospital service in relation to the total is about what would be expected in a general hospital. Knowledge of the exact relation becomes of value in actual operation in prorating bank debits over the various services. Actually the number of transfusions given in the pediatric service is much higher than is stated. The figure expressed represents the number of units or half-units issued from the bank and does not take into account the fractional transfusion of some units, a practice most common in the pediatric service.<sup>3</sup>

2. Schiff, L.; Stevens, R. J.; Goodman, S.; Garber, E., and Lublin, A.: Observations on the Oral Administration of Citrated Blood in Man, *Am. J. Digest. Dis.* 6:597, 1939.

3. In this report the number of transfusions corresponds to the number of units and half-units of blood issued from the blood bank. Actually the number of transfusions was larger, because some of these were divided and given as multiple transfusions.

TABLE 5.—*Transfusions from Blood Bank (Jan. 1, 1939, to Feb. 23, 1940)*

Group	White (68.9%)		Negro (31.1%)		Both Races	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
AB.....	41	2.0	23	2.4	64	2.1
A.....	915	43.1	274	28.7	1,189	38.6
B.....	162	7.6	177	18.5	339	11.0
O.....	1,003	47.3	482	50.4	1,485	48.3
Total.....	2,121	100.0	956	100.0	3,077	100.0

## COMMENT

Three thousand and seventy-seven units and half-units of blood were issued from the bank and given in transfusion. The distribution of these units and half-units according to race and to the four blood groups is recorded in table 5.

TABLE 6.—*Transfusions of Unlike Groups*

Groups	Number	Per Cent
O—B.....	31	26.7
O—A.....	50	43.1
O—AB.....	1	0.9
A—AB.....	18	15.5
B—AB.....	16	13.8
Total.....	116	100.0
Total transfusions of unlike groups.....	116	3.8
Total transfusions of like groups.....	2,961	96.2
Total transfusions in series.....	3,077	100.0

## COMMENT

Of the 3,077 transfusions given, 2,961, or 96.2 per cent, represented transfusions of like groups. In only 3.8 per cent of the cases was the bank unable to supply the group requested. The universal donor and universal recipient principle was applied in each of the 116 cases in which it was necessary only after a preliminary direct match, the Coca compatibility test being used.<sup>4</sup> In the absence of group AB blood, group A or group B blood was always selected in preference to group O, because only one incompatible agglutinin-agglutininogen complex is dealt with in the dilution principle.

TABLE 7.—*Incidence of Transfusion Reactions*

	Number	Per Cent
Transfusions.....	3,077	100.0
Reactions.....		
Hemolytic.....	2 *	0.06
Febrile.....	125	4.06
Urticarial.....	56	1.82
Total.....	183	5.94

\* One questionable.

4. Hoxworth, P., and Ames, A.: Blood Grouping and Compatibility, J. A. M. A. 108:1234 (April 10) 1937.

TABLE 8.—*Types of Transfusion Reactions*

	Number	Per Cent
Hemolytic ..	2 *	1 1
Febrile with chill.	95	
Febrile.....	30	68 2
Mild urticarial...	53	
Severe urticarial.	3	30 6
Total	183	100 0

\* One questionable

## COMMENT

Any report on the incidence of unfavorable transfusion reactions must necessarily be affected by the author's definition of a transfusion reaction. Subjective complaints not accompanied with any related objective, clinical or laboratory abnormalities during or after the transfusion have been disregarded in this presentation. All reactions occurring in this series are classified as hemolytic, febrile or urticarial. Untoward reactions occurred after 5.94 per cent of the 3,077 transfusions given. Of the two hemolytic transfusion reactions reported, one was the result of a laboratory error in which group A blood was given to a person whose blood was group O, and the other, which is not well established, resulted from the transfusion of group A blood to a person whose blood was group A. The following reports present the clinical and laboratory data in each instance.

## REPORT OF CASES

CASE 1.—A white man aged 55 years, with pyloric obstruction due to a duodenal ulcer, received a preoperative blood transfusion on Aug. 1, 1939. Blood of group A was given to the patient, whose blood group was later determined as O. The laboratory technician had, by mistake, performed the grouping and compatibility tests on a specimen of group A blood which had become confused with the specimen from the patient. Approximately 75 cc. of citrated blood had been given when the patient suddenly complained of precordial pain and a sensation of tingling in both lower extremities. The transfusion was stopped at this point. Pallor and dyspnea were noted; the radial pulse could not be felt, and the systolic pressure fell to zero. There were vomiting and diarrhea. Treatment for shock was instituted, and the blood pressure rapidly rose to 150 systolic and 110 diastolic. A severe shaking chill occurred twenty minutes later, followed by cyanosis. The patient was placed in an oxygen tent, and his general condition was good from that time on. Five hours after the transfusion he complained of cramps in the gastrocnemius muscles. Twelve hours after the transfusion he voided urine for the first time; 150 cc. of dark brown, smoky urine was passed. Examination of the urine revealed a 4 plus benzidine reaction, a few granular casts, a 3 plus reaction for albumin, a specific gravity of 1.015 and a  $pH$  of 6. The urinary abnormalities gradually disappeared over a period of three days. On the day following the transfusion the urea nitrogen content of the blood was 40 mg. per hundred cubic centimeters. One day later, the value was 26 mg. per hundred cubic centimeters and the carbon dioxide-combining power was 49 volumes per cent. On the third day the value for urea nitrogen was 25 mg. per hundred cubic centimeters, and the carbon dioxide-combining power was 59 volumes per cent. The blood chemistry was normal on the fourth day. Two days later, on August 7, a subtotal gastric resection was performed, and the postoperative course was uneventful.



CASE 2.—A white woman aged 34 was admitted to the medical service on Jan. 5, 1940. A diagnosis of chronic myelogenous leukemia had been established in July 1938. On admission to the hospital the patient was complaining of pain in the chest and in the left upper abdominal quadrant, severe coughing and gross hemoptysis. Examination revealed rales over both lung fields and a pleural friction rub over the base of the left lung. The spleen was palpable and tender. A clinical impression of pulmonary and splenic infarction was made. During the next two days the general course was progressively downhill, with a temperature of 104 to 105 F., a pulse rate ranging from 140 to 150 and a respiratory rate varying from 30 to 40, accompanied with cyanosis. The red blood cell count fell from 3,700,000 per cubic millimeter on admission to 2,510,000 on the fourth day in the hospital. The patient appeared moribund on the fifth day, when a transfusion of 300 cc. of citrated blood was given. Three and one-half hours later she complained of severe generalized abdominal pain and progressed almost immediately into a state of profound shock. A specimen of urine voided just before the onset of abdominal pain was recorded as dark red and gave a strongly positive reaction to benzidine. Death followed fifteen minutes after the occurrence of abdominal pain.

Permission for autopsy was not obtained, and unfortunately, the transfusion service did not learn of the death until twenty-four hours later, at which time the body had been embalmed. For these reasons laboratory and tissue studies sufficient to prove a diagnosis of hemolytic transfusion reaction were not possible.

#### COMMENT

In case 2, the blood groups of the donor and the patient prior to transfusion were determined as A. There was no evidence of incompatibility on the direct match test. Reexamination of the specimens of blood obtained before transfusion revealed that the blood of the patient belonged to subgroup A<sub>2</sub> and that of the donor to subgroup A<sub>1</sub>. The specimens were then sent to Alexander Wiener, serologist and bacteriologist in the office of the chief medical examiner of New York city. Results of his examination also showed the blood of the patient to belong to subgroup A<sub>2</sub> and that of the donor to subgroup A<sub>1</sub>. Wiener also found the blood of the patient to be Rh + and that of the donor to be Rh — and stated that this agglutinin therefore could not have played any role in the reaction. He concurred with the opinion that a hemolytic transfusion reaction was not proved and stated that if this were a transfusion reaction it would have to be considered an unexplained one not avoidable by any of the technics available at present. This case is reported because the death was the only one in the entire series which might be attributed to the transfusion of blood.

Because of the known susceptibility of patients suffering from leukemia to severe transfusion reactions, some authorities on blood transfusion consider leukemia a contraindication to blood transfusion.<sup>1</sup>

In reporting this series of transfusions the following case is also of interest.

CASE 3.—A white man aged 32 years received a transfusion one hour after appendectomy for acute appendicitis with perforation. The patient's blood was of group A, and he had received 300 cc. of group B blood issued from the bank by mistake before the technician had realized the error. No signs of immediate or delayed reaction, subjective or objective, developed, despite close watching of the patient. All post-transfusion urinary specimens were examined for six days; there was no evidence of hemoglobinuria. The patient was discharged from the hospital on the twentieth postoperative day and was seen one month later in the follow-up clinic. No ill effects resulted from the transfusion of incompatible blood. Recheck of both the pretransfusion and the post-transfusion specimens of blood showed that of the patient to be group A and that of the donor to be group B. The incompatibility on direct match was evident in both specimens.

Febrile reactions followed 125 transfusions in this series, a percentage of 4.06. In 95 cases the rise in temperature was preceded by a chill. There were no deaths of which these reactions were considered a contributory cause. In 53 cases urticarial reactions marked only by the appearance of wheals followed close on transfusion. In 3 cases widespread urticaria was preceded by pallor, sweating, a marked increase in pulse rate and a fall in blood pressure. Each of the patients responded readily to supportive measures instituted for anaphylactic shock.

The incidence of urticarial reactions might be reduced if blood were drawn from donors in a fasting state. The difficulty and inconvenience of obtaining such donors make this plan impracticable, particularly in view of the mildness and infrequency of urticarial reactions.

TABLE 9—*Febrile Reactions in Relation to Groups Transfused*

Groups	No of Cases	Reactions	Febrile	Per Cent
AB—AB	64	3	2	3 1
A—A *	1,171	73	56	4 7
B—B..	323	23	16	4 9
O—O ...	1,403	73	47	3 3
O—AB .	1	0	0	0
B—AB ..	16	2	2	12 5
O—A... ..	49	1	1	2 0
O—B... ..	31	1	1	3 2
A—AB . . .	18	0	0	0

\* A—A series corrected for patient No 78995

A—A transfusions 1,171 — 60 = 1,111

A—A febrile reactions 56 — 11 = 45

Corrected determination  $45/1,111 = 4.0$  per cent.

TABLE 10—*Data on a Patient (Blood Group A) with Chronic Lymphatic Leukemia*

	Number	Per Cent
Transfusions given. ....	61	
Transfusions of group A blood	60	
Transfusions of group O blood .	1	
Febrile reactions .....	12 *	19 7
Urticarial reactions ...	6	9 8
Total reactions.....	18	29 5

\* One reaction was O—A

## COMMENT

The causes of chills and fever which follow intravenous administration of solutions, including blood, and methods for reducing the incidence of these reactions have been a subject of much interest in many hospitals. The adoption of rigid routines in the preparation of solutions and cleansing of glassware and tubing with which the solutions come in contact have reduced the incidence of untoward reactions. Despite careful attention to these factors, the incidence of chills and fever in most reported series of blood transfusions varies from 5 per cent to 20 per cent. In addition to extrinsic factors it is probably true that the condition of the patient plays a role in causation of these reactions. It is a matter of common observation that patients in severe septic states and with leukemia, for example, are much more subject to post-transfusion chills and fever.

Recently some writers<sup>5</sup> have contended that the subgroups of A and AB, namely,  $A_1$ ,  $A_2$ ,  $A_1B$  and  $A_2B$ , when mixed in transfusions, may be responsible for post-transfusion chills and fever. For this reason the transfusions in this series were analyzed from the standpoint of febrile reactions in relation to blood groups transfused. The incidence of febrile reactions was 4.7 per cent between members of group A, 4.9 per cent between members of group B and 3.3 per cent between members of group O. While the percentage of reactions occurring among members of group A was no higher than that observed among members of group B, both of these series revealed a higher percentage than occurred among members of group O. It may be that the number of transfusions given members of group B is not sufficiently large to permit any value to be attached to a percentage analysis. Considering this, the incidence of reactions among 1,171 transfusions of group A blood to group A patients (4.7 per cent), as compared to those in which group O was concerned (3.3 per cent), is considerably higher. However, in the group A series, 1 patient received sixty-one transfusions for anemia secondary to chronic lymphatic leukemia. Febrile reactions followed twelve of the sixty-one transfusions, and urticarial reactions followed six, making a total of eighteen. The total incidence of reactions was 29.5 per cent and that of febrile reactions 19.7 per cent. One of the febrile reactions followed a transfusion of group O blood, leaving eleven febrile reactions in sixty transfusions of group A blood. A truer analysis of the group A reactions results if the series is corrected by eliminating the transfusions and reactions of this patient, since in the group O series no patient particularly susceptible to reactions received a comparable number of trans-

5. Davidsohn, I.: A Method for Recognition of Blood Subgroups  $A_1$  and  $A_2$ , J. A. M. A. **112**:713 (Feb. 25) 1939. Blinow, N. I.: Subgroups  $A_1$  and  $A_2$  and Their Practical Significance, Sovet. khir. **7**:335, 1934.

fusions. The corrected reaction rate in the group A series is 4 per cent, which is very close to the rate of 3.3 per cent in the group O series, and the difference is not significant, being well within the limits of statistical error when the number of cases reported is considered.

TABLE 11—*Relation of Reactions to Age of Blood Transfused*

Age of Blood in Days	Number of Trans- fusions	Febrile		Urticarial	
		Number	Per Cent	Number	Per Cent
1 . . . . .	463	21	4.5	19	4.1
2	510	25	4.6	9	1.1
3	386	13	3.4	5	1.3
4	286	10	3.5	2	0.7
5	248	13	5.2	5	2.0
6	230	10	4.3	4	1.7
7	182	6	3.3	2	1.1
8	140	5	3.6	3	2.1
9	110	2	1.8	1	0.9
10	93	4	4.3	1	1.1
11	99	4	4.4	3	3.0
12	64	2	3.1	0	0
13	55	2	3.6	1	1.8
14	56	2	3.6	1	1.8
15	29	1	3.5	0	0
16	20	2	10.0	0	0
17	16	2	12.5	0	0
18	7	1	14.3	0	0
19	5	0	0	0	0
20	2	0	0	0	0
21	1	0	0	0	0
Total	3,077	125		56	

#### COMMENT

Whether the incidence of reaction increases as bank blood ages is another subject of much interest. Because of this the transfusions given in this series are analyzed from the standpoint of reactions in relation to the age of the blood given. This analysis will become of real value as more statistics are accumulated. At present the figures indicate that the aging of blood does not increase the incidence of reactions.

Another point of interest shown in this analysis is that in practical operation the great majority of bank blood units given are under 7 days of age. Thus the age limitations of bank blood, which have been fairly well established, can be met without difficulty.

#### SUMMARY AND CONCLUSIONS

An analysis of the experience gained and statistics derived from 3,077 transfusions of bank blood at the Cincinnati General Hospital is presented. This was made in order to study the effects of transfusion of preserved blood and also to provide information helpful in the actual operation of a blood bank.

The results may be summarized as follows:

1. Blood of the same group as that of the patient is available without delay in 96 per cent of the cases.

2. The incidence of untoward transfusion reactions compares favorably with that in reported series of transfusions of fresh blood.

3. Aging of blood does not increase the incidence of febrile reactions.

4. There is no significant increase in untoward reactions resulting from transfusion of group A blood as compared with transfusion of blood of the other groups.

5. The causes of loss of bank blood are, in order, positive reactions for syphilis, expirations of the time limit and clotting. Methods for minimizing these losses are suggested.

6. In the 3,077 transfusions of blood given, only 1 death occurred which might be attributed to the transfusion.

# RESECTION OF THE COLON BY INTUSUSCEPTION

A ONE STAGE INTERIORIZATION PROCEDURE RESULTING IN AN  
END TO END ANASTOMOSIS

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More than two hundred and seventy-five technical procedures<sup>1</sup> have been devised to diminish the amount of contamination of the peritoneal cavity incidental to resection of portions of the large bowel. The fact that no method has yet proved entirely satisfactory has led to attempts to reduce the risk of infection by measures directed toward increasing the resistance of the patient. These attempts have consisted for the most part of more careful preoperative preparation of the patient, use of intraperitoneal injections designed to increase local immunity and more widespread use of multiple stage operations.

In general, the technical procedures for extirpation of a portion of the colon with subsequent reestablishment of intestinal continuity may be divided into two groups. In one group, the peritoneum and the bowel are opened at the same time, and the various technics are directed toward securing the least possible amount of soiling, either by appropriate isolation of the open bowel with towels and sponges or by keeping the bowel temporarily closed by various methods until after the anastomosis has been completed.

The object of the technics employed in the second group is to have both the resection and the subsequent restoration of continuity of the bowel performed at a time when the peritoneum is not open. This is accomplished by extra-abdominal exteriorization of the offending lesion, with delayed resection and subsequent anastomosis by gradually crushing the spur between the two limbs of the fecal fistula.<sup>2</sup>

The fundamental difference between these two groups of procedures lies in the fact that with immediate resection and anastomosis the spread

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Aided by a grant to Vanderbilt University from the Division of Medical Sciences of the Rockefeller Foundation.

1. Poth, E. J.: A Clean Intestinal Anastomosis, *Arch. Surg.* **28**:1087 (June) 1934.

2. Bloch, O.: On Extra-Abdominal Treatment of Intestinal Cancer, *Nord. med. ark.* **24**:1, 1892. Paul, F. T.: Colectomy, *Brit. M. J.* **1**:1136, 1895. Von Mikulicz, J.: Small Contributions to the Surgery of the Intestinal Tract, Boston M. & S. J. **148**:608, 1903.

of bacteria from the lumen of the intestine starts at the same time that fibrinous agglutination of the opposed serous surfaces begins, so that occasionally the establishment of an effective fibrinous barrier may be delayed and postoperative intraperitoneal leakage of intestinal contents may ensue. In the exteriorization type of procedure, this fibrinous barrier is established before the spread of bacteria begins and therefore the danger of intraperitoneal contamination is considerably diminished.

Because of this fundamental difference, the exteriorization procedures possess certain physiologic advantages which could never be attained by the methods involving immediate resection and anastomosis. Unfortunately, they also have numerous well known disadvantages, such as inability to resect widely the mesentery and the presence of a temporary artificial anus, which tend to restrict their general use.

In considering both the advantages and disadvantages of these two methods, one realizes that the ideal procedure would be a combination of the two, that is, an intrainestinal interiorization of the lesion, with delayed necrosis of the interiorized portion resulting in an end to end anastomosis.

This ideal (resection with anastomosis) is occasionally accomplished by nature as the result of spontaneous intussusception of a lesion of the colon, with subsequent slough of the intussusceptum. Unfortunately, such a favorable result is not often observed, because of the disastrous effects of strangulation and intestinal obstruction. For this reason, operative reduction of the intussusception is usually attempted for conditions which do not respond to conservative therapy.

It is interesting to note the frequency with which this spontaneous sloughing of an intussusceptum occurred before the advent of modern abdominal surgery. In 1874, Leichtenstern<sup>3</sup> reported a series of 593 cases of intussusception, in 29 per cent of which there were spontaneous necrosis and elimination of the intussusceptum. Of the 170 cases of "spontaneous elimination," 149 were followed over a sufficient period to determine that recovery occurred in 59 per cent.

In spite of the rather obvious dangers of spontaneous intussusception, limited clinical application of nature's method of resection has previously been attempted in a virtually unmodified form. Thus, in 1895 Guinard<sup>4</sup> reported 2 cases in which he had invaginated segments of the small intestine. In the first of these, 9 cm. of gangrenous bowel was invaginated, and in the second, two gangrenous rings of intestine which had been located at the neck of the sac of a strangulated hernia were invaginated. The patients in both cases recovered. In 1908,

3. Leichtenstern, O.: Ueber Darm-Invagination: III, Vrtljschr. f. d. prakt. Heilk. 121:17, 1874.

4. Guinard, A.: Traitement des hernies gangrenées par l'invagination totale ou partielle, Assoc. franç. de chir., Proc.-verb. 9:455, 1895.

Summers<sup>5</sup> described 2 cases of annular gangrene of the small intestine treated by invagination, and in 1927 he referred to 5 additional cases in which this method was used. There were 2 deaths in this series of 7 cases. He stated that he restricted his use of the method to cases in which the invaginated portion would not exceed 5 cm. in length, because of a fear of intestinal obstruction and of difficulty in producing the invagination. In both Guinard's and Summers' cases the arterial blood supply of the bowel which was invaginated was already so affected that further changes resulting from strangulation could not occur. This probably accounts for their success.

It would seem that successful development of this natural intussuscepting type of intestinal resection would depend on (1) avoidance of strangulation; (2) prevention of intestinal obstruction; (3) development of a method by which an intussusception might be readily produced, and (4) utilization of some method assuring delayed amputation of the intussusception.

The dangers of strangulation may be greatly diminished by removal of the mesocolon from the bowel which is to be invaginated. Intestinal obstruction may be avoided and invagination of the bowel easily produced by the appropriate use of a rubber tube, the technic of which is described subsequently. Although spontaneous necrosis would result in amputation of that portion of the bowel which was deprived of its blood supply through division of the mesentery, delayed amputation of the intussusceptum at points proximal to this level of viability may be obtained by occlusion of the intramural blood supply with an elastic ligature.

#### TECHNIC

The accompanying illustrations are designed to show the important steps of this operation as it is performed on the dog. The ileocecal region was chosen because it would seem to offer those difficulties which would probably be encountered in man. Thus, it is the région of the colon most distant from the anus; the dog's appendix affords a considerable bulk for invagination, and it could be shown that in this animal, at least, a tube can be passed through the ileocecal valve for a considerable distance into the ileum.

The following paragraphs are devoted to a description of the technical details of this procedure. For the sake of simplicity, these details are presented in sections corresponding roughly to the steps shown in the illustrations.

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5. Summers, J. E.: Invagination of Limited Annular Gangrene of the Small Bowel Versus Resection, *J. A. M. A.* **51**:472 (Aug. 8) 1908; The Treatment of Annular Gangrene of the Small Bowel by Invagination Versus Resection, *Surg., Gynec. & Obst.* **44**:374, 1927.



1. The immediate preparation for operation consists of thorough cleansing of the bowel distal to the segment to be resected and construction of the tube which is to be used both for production of the intussusception and relief of postoperative distention of the bowel proximal to the intussusception.

The rubber tube which was used in the experimental evolution of this technic was the one most convenient at the time. It was made of ordinary hard red rubber suction tubing approximately 1 cm. in diameter. In its preparation two rather prominent rolls of adhesive tape, designed to hold the initial, "intussuscepting" ligature, are placed on the tube, far enough from its end to insure protrusion of the tube into the proximal portion of the bowel after completion of the intussusception. This distance is usually approximately two thirds of the expected length of the segment of bowel to be resected. Near the end of the tube are placed several smaller rolls of adhesive tape to prevent slipping of the final necrotizing ligature when the intussusception is doubled over it. The latter rolls are an accessory rather than a necessity (fig. 1).

At operation the segment of bowel to be resected is mobilized, and its mesentery is removed. This preliminary resection of the mesentery not only eliminates subsequent strangulation, with its concomitant intestinal obstruction, but enables the operator to carry out the necessary manipulations of the bowel on a segment which has been both denervated and devascularized, thus eliminating this manipulation as a possible source of surgical shock. Clinically it might also be thought of as a prophylactic measure against possible metastasis of embolic tumor.

An assistant passes the tube by rectum until it is felt near the peritoneal reflection of the rectum by the operator. The latter then directs the end of the tube up the colon and assists it in its passage through the segment to be resected. When passage of the tube has been completed, the two larger rolls of adhesive tape should be so situated that the interval between them will be approximately 2 to 3 cm. proximal to the center of the loop to be resected. This adds sufficient length to the outer layer of the intussusceptum to permit doubling of the intussusception after the application of the final necrotizing ligature.

A ligature of umbilical tape is then placed about the bowel and tied so that it lies in the space between the two larger rolls of adhesive tape (fig. 1). Umbilical tape or similar relatively broad ligature material is used for this purpose because adequate friction can be obtained without tying the ligature tight enough to diminish the lumen of the tube.

2. After the bowel has been anchored to the tube, the portion of the segment distal to the ligature is grasped by the operator, and downward traction is applied to the anal end of the tubes by an assistant (fig. 2 *A*). An intussusception is readily produced and increased to a point at which the base of the intussusception is approximately 1.5 to 2 cm. from the mesenteric borders. The reason for stopping the intussusception at this point is to leave sufficient viable bowel above the base of the intussusception for completion of the anastomosis.

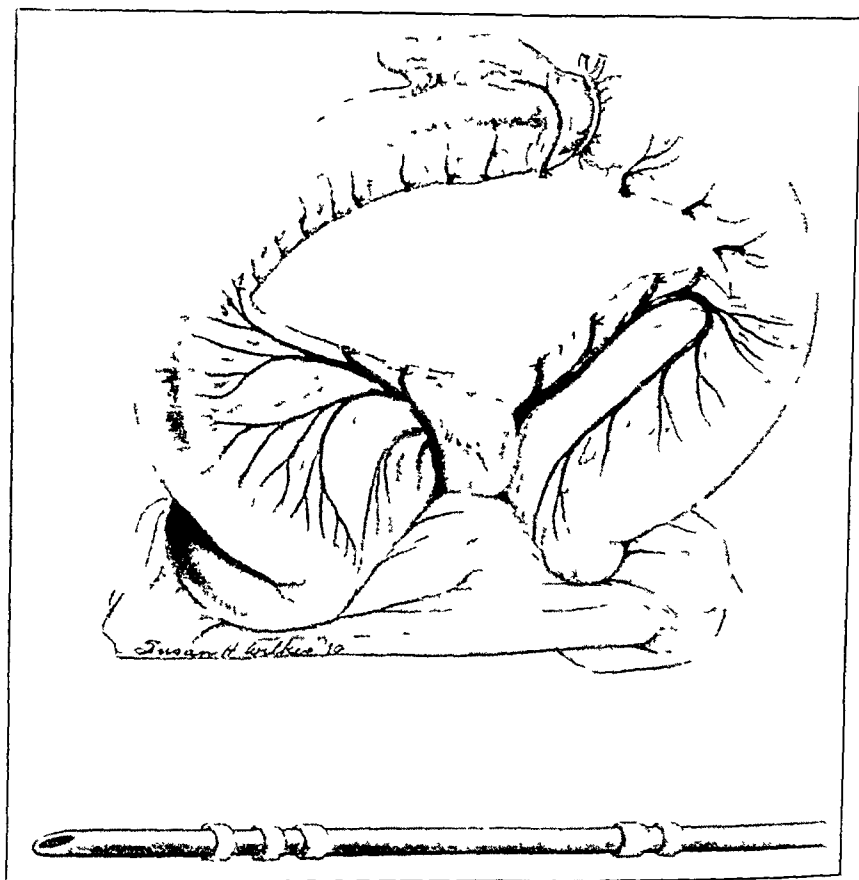


Fig 1.—The mesentery of the segment to be resected has been removed. A rubber tube has been passed by rectum through this segment and a ligature tied about the bowel between two narrow rolls of adhesive tape on the indwelling tube. This ligature should be slightly proximal to the midportion of the segment to be resected. The rubber tube with the rolls of narrow adhesive tape in place is shown at the bottom of the picture.

3. Another ligature of umbilical tape is tied about the base of the intussusception to maintain it and subsequently serve as a fixed apex for the second intussusception. Care should be exercised in the placement of this ligature, so that the smallest possible lip of the intussus-

cipiens is proximal to it (fig. 2 *B*). If the ligature should fall just distal to one of the smaller rolls of adhesive tape, it will help considerably in the next step (doubling the intussusception), for the small roll of adhesive tape will impinge on the ligature when downward traction is made. However, this is not essential for effective doubling of the intussusception.

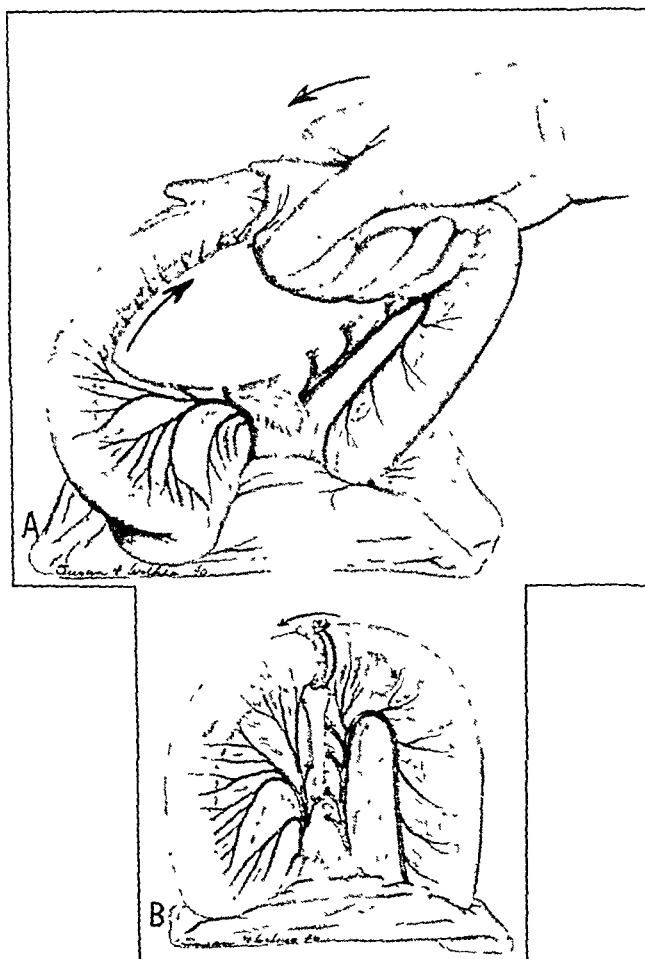


Fig. 2.—*A*, downward traction on the anal end of the indwelling tube by an assistant, together with countertraction on the intussusciens by the operator, readily produces an intussusception. *B*, the initial intussusception has been completed to within approximately 2 cm. of the mesenteric borders, and the necrotizing ligatures have been tied about its base. The arrow shows how the bowel is to be reintussuscepted over these ligatures.

Although it would appear at first that this ligature would be sufficient to produce necrosis of all the intussusceptum distal to it, experience has shown that it does not invariably do so. Therefore, a rubber

band is also tied snugly about the base of the intussusception. This effectively amputates the intussusceptum through all of its layers. Use of the rubber ligature alone is not advisable, because it has a tendency to roll when the intussusception is doubled over it and may thus considerably complicate a simple maneuver. I should also like to warn specifically against the application of crushing clamps to the base of the intussusception, for in several instances in which it was tried slight leakage of gas and fecal material from the crushed area was noted on removal of the clamps.

4. After the necrotizing ligatures have been placed, the bowel is grasped as before, and further traction is applied to the rectal tube.

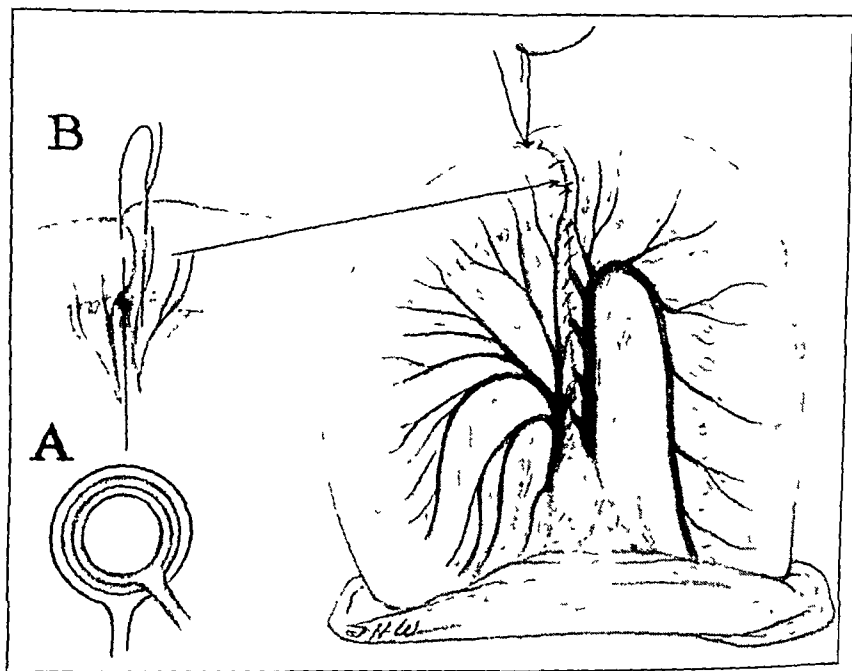


Fig. 3.—The second intussusception has been produced and interrupted sub-mucosal sutures placed between the bowel above and the intussusciens below. One of these sutures is left long so that it may later be sewed to the parietal peritoneum to forestall any further intussusception. A second row of anastomotic sutures is placed about the circumference of the bowel (not shown). The defect in the mesentery has been repaired. *A*, cross section of the anastomosis, showing nonapposition of the mesenteric borders. *B*, simple right angle suture used to secure serosal approximation in this type of anastomosis.

This produces another, very short intussusception over the two ligatures at the base of the first intussusception; that is, a double intussusception is produced with the apex of the second, short, viable intussusceptum, being marked by the ligatures which are destined to produce necrosis of the first, relatively long intussusceptum. Successful completion of

the anastomosis is dependent on securing accurate approximation of the serosal surfaces of the layers of this short intussusceptum.

MacFee<sup>6</sup> and others have drawn attention to the importance of carefully removing the fat from the surfaces to be approximated as well as carefully ligating all vessels in the line of anastomosis. In so doing one also removes a relatively large portion of the serosa, the fat lying for the most part between the leaves of the mesentery at the point where they separate to envelop the bowel. This removal of fat and serosa from the wall of the bowel results in an increase in the normally present "bare" area at the mesenteric border, and, because of the loss of the specific adhesive characteristic of peritoneum, approximation of two such "bare" areas would theoretically be expected to increase the danger of postoperative leakage. In this connection, Mayo<sup>7</sup> stated: "I have watched surgeons use great care to keep the mesenteric attachments adjusted exactly to each other in making an end to end anastomosis of the intestine. This leaves two fat areas, without peritoneum, joined to each other. If the bowel is rotated a quarter of an inch, an area with perfect peritoneal protection is joined to an area that has no such protection, union is immediate, and peristalsis is not interfered with in any way." This principle of contra-rotation of the mesenteric borders seems to eliminate the "bare" areas as possible regions of ineffective fibrinous agglutination (fig. 3 *A*).

The problem of approximating sutures in this intussuscepting type of anastomosis is somewhat different from that encountered in the conventional end to end anastomosis, for whereas in the latter the prime purpose is the abutment of two surfaces at right angles to the long axis of the bowel, in this type the desired effect is an approximation of two serosal surfaces which lie in a plane parallel to the long axis of the bowel. Thus, for example, although the Halsted square mattress suture is ideally suited for abutment, it is not so satisfactory for approximation in parallel.

In securing the latter type of approximation, I have found the simple right angle suture to be extremely easy to place and entirely satisfactory (fig. 3 *B*). In its application, care is taken to secure a bit of the submucosa, and penetration into the lumen is guarded against.<sup>8</sup> One of the first row of interrupted sutures is left long so that later it may be attached to the parietal peritoneum to forestall any further intus-

6. MacFee, W. F.: Resection with Aseptic End-to-End Anastomosis for Carcinoma of the Colon, *Ann. Surg.* **106**:701, 1937.

7. Mayo, C. H.: Wrinkles and Recipes in Intestinal Surgery, *Ann. Surg.* **98**: 830, 1933.

8. Halsted, W. S.: Circular Suture of the Intestine: An Experimental Study, *Am. J. M. Sc.* **94**:436, 1887; *Surgical Papers*, Baltimore, Johns Hopkins Press, 1924, vol. 1, p. 185.

susception. For the second row of anastomotic sutures I have used the Cushing continuous right angle suture around the entire circumference of the bowel. Martzloff, Moore and Gardner,<sup>9</sup> in a large series of experimental intestinal anastomoses, have reported that the incidence of postoperative leakage was considerably less with silk than with other types of suture material. Therefore, only silk has been used in this series of resections.

After completion of the anastomosis, the operation is finished in the usual manner. The mesenteric borders are approximated; an

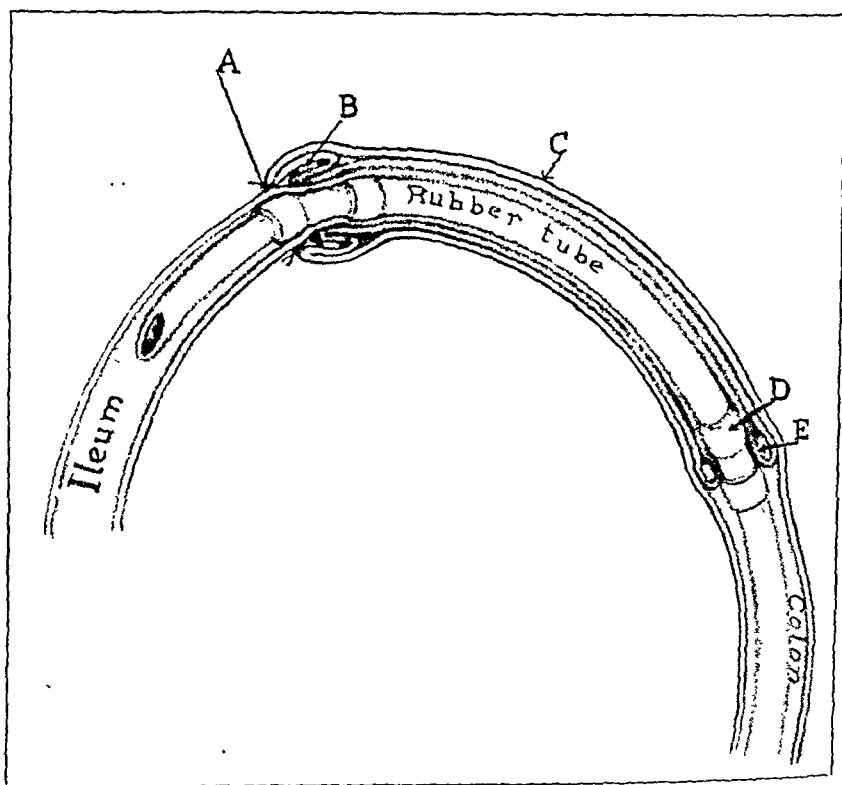


Fig. 4.—Diagram of a longitudinal section through the completed anastomosis. A, serosal approximating sutures; B, necrotizing ligatures which will produce necrosis of the shadowed intussusceptum (B to E); C, the intussusciens; D, rolls of adhesive tape on the indwelling rubber tube, which serve to hold the initial ligature; E, initial, or "intussuscepting," ligature.

opening is made in the omentum, and the uncut suture from the first row of anastomotic sutures is pulled through. This is then sewed to the parietal peritoneum, and the anastomosis is protected with omentum.

9. Martzloff, K. H.; Moore, P. H., and Gardner, J.: Aseptic End-to-End Intestinal Anastomosis: A Report of One Hundred and Ninety-Seven Experimental Anastomoses in Dogs, *West. J. Surg.* 47:611, 1939.

The abdomen is closed, and the excess of rubber tubing which protrudes from the anus is removed. In dogs it has not been found necessary to fix the tube to the anal margin; it is left free and allowed to pass when the necrotizing ligature at the base of the initial intussusception cuts through.

#### EXPERIMENTAL RESULTS

This technic for resection of the bowel has been employed on 16 dogs. There were no early postoperative deaths, and convalescence

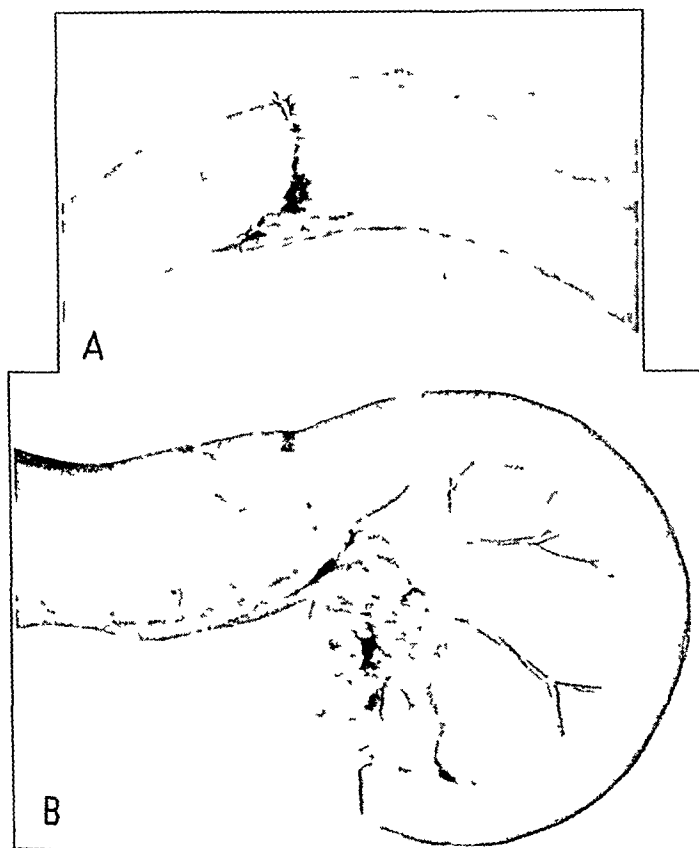


Fig. 5.—*A*, photograph of a specimen removed eight days after operation. *B*, photograph of a specimen removed thirty-three days after operation.

was uneventful in every instance. One dog died twenty days after the operation, of distemper, and another, rather old dog died forty-six days after operation, from an undiscovered cause. The peritoneal cavities in both of these dogs were free from infection; the anastomoses were in good condition, and there was no evidence of intestinal obstruction. The other dogs were killed for specimens at varying intervals after operation. In none was there any evidence of peritoneal inflammation or obstruction, but in most there was an omental adhesion about the

suture which had been sewn to the parietal peritoneum. A few of these specimens are shown in the accompanying illustrations (figs. 5, 6 and 7).

Eleven operations were performed in which the resected area included the ileocecal region and five in which the resected area was limited to different segments of the descending colon (there is no sigmoid flexure in the dog). Thus it was possible to vary the amount of bowel resected and the location of the anastomosis over a very wide range. The amount resected varied from resections of the colon and the terminal portion of the ileum in which the segment was between 3 and 4 feet (0.9 to 1.2 M.) in length to very limited resections of only a few centimeters. The location of the anastomosis varied from just distal to the ileocecal region to beneath the peritoneal reflection of the rectum.

After recovery from the intravenous pentobarbital sodium anesthesia, the dogs were allowed to take food or water as they desired.

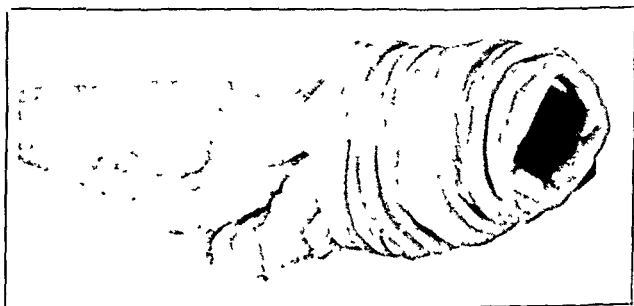


Fig. 6.—Photograph of a specimen removed twenty days after resection of approximately 10 cm. of descending colon. The distal portion of the colon has been folded back to show the stoma of the healed anastomosis.

There was a latent period of several hours during which there was little, if any, drainage from the indwelling rectal tube, and then drainage began, continuing until the tube was extruded.

Necrosis of the intussusceptum usually became apparent within twelve hours after operation. With resections in which the intussusceptum remained entirely within the bowel gradual autolysis took place, so that the dogs would often pass small quantities of thin black fluid around the rectal tube. With resections in which the apex of the intussusceptum protruded through the anus the exposed portion became increasingly dark, shrinking gradually until a typical dry gangrene resulted.

The indwelling rectal tube was usually retained for thirty-six to forty-eight hours, but in a few instances, in which the animals were restrained so that they did not have impulses to defecate, this period was considerably longer. Extrusion of the tube was usually accom-



panied by a bowel movement, the excreta consisting of the fluid accumulated from autolysis of the intussusceptum together with incompletely digested strips of necrotic bowel. On the extruded tube would be found the various ligatures that had been tied about the bowel at operation.



Fig. 7.—Photomicrograph showing the site of anastomosis in a specimen removed forty-nine days after operation. Hematoxylin and eosin;  $\times 7$ .

After passage of the tube, normal intestinal habits were usually restored, but in a few instances, in which total colectomy had been performed, there was diarrhea which lasted for several weeks, with gradual return toward normal. In these animals the perianal region often became moderately excoriated.

## COMMENT

A new method of resection and anastomosis of the colon based on intussusception has been evolved. Fundamentally the procedure consists of an intrainstestinal interiorization of the segment to be resected into the lumen of the bowel distal to it and subsequent slough of the interiorized portion as a result of ischemia. It combines all of the advantages of the usual extra-abdominal exteriorization procedure,<sup>1</sup> with the obvious advantages of an end to end anastomosis and, at the same time, eliminates most of the disadvantages of both. Not only is operative soiling completely eliminated, but the danger of postoperative leakage is reduced to a minimum through delay in exposure of the anastomosis to fecal contamination. At the same time, the possibility of intestinal obstruction is avoided by use of an indwelling rubber tube.

Unfortunately, I have not yet had an opportunity to apply this method clinically, but I may predict to a certain extent what its indications and contraindications will be. Primarily, of course, its application will be limited to lesions which can be intussuscepted into the bowel distal to them. This implies not only that the lesion must be small enough to enter the bowel distal to it but that the character of the intestinal wall must be such that invagination may be accomplished. This immediately eliminates large, bulky lesions and those in which there is such a degree of intramural fibrosis as to preclude the folding-back process necessitated by the invagination. It is possible, however, that a fair percentage of medium to small tumors of the colon will be resectable by this procedure, as well as many lesions of prefibrotic ulcerative colitis, diverticulosis and multiple polyposis.

Although this type of resection of the colon is designed as a one stage interiorization operation, I should like to emphasize that the presence of obstruction or subacute perforation still necessitates preliminary diversion of the fecal stream proximal to the region to be resected, together with the lapse of sufficient time to insure minimal chances of contamination from the pericolic inflammatory tissue on mobilization.

The range of application of this method of resection of the colon should increase in proportion to the increase in the number of early diagnoses of colonic lesions.

## SUMMARY

An intussuscepting type of resection of the colon has been developed. This is a one stage intrainstestinal interiorization procedure, which embodies the following steps: 1. The segment to be resected is mobilized and its mesentery removed. 2. A fairly stiff rubber tube is passed by rectum through this segment and anchored to the tube with a ligature. 3. Traction on the tube from below coupled with countertraction

on the intussusciens from above readily produces an intussusception. 4. This intussusception is increased to within 1.5 to 2 cm. of the mesenteric borders, and a necrotizing ligature is tied about its base. 5. With this ligature as its apex, another, very short intussusception is produced in the same manner as the first, and serosal approximating sutures are placed between the bowel above and the intussusciens below.

This technic for resection of the colon seems to preserve the asepsis of the usual extra-abdominal exteriorization procedure and at the same time presents the advantages of an end to end anastomosis, for in its use the lumen of the bowel is not opened, and exposure of the suture line to fecal contamination is deferred until the intussusceptum becomes necrotic prior to its spontaneous amputation.

This method for resection and anastomosis of the colon has been employed in 16 dogs. There were no early postoperative deaths, and convalescence was uneventful in every instance.

Dr. Alfred Blalock has given valuable suggestions and constructive advice during this study.

# POSTOPERATIVE HYPOPROTHROMBINEMIA AND ANESTHESIA

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AND

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It is generally agreed that a reduction of the prothrombin content of the plasma frequently is seen during the postoperative period in patients with biliary fistula or obstructive jaundice. Such a reduction may occur even though preoperative correction of any prothrombin deficiency has been carried out through the medium of vitamin K and bile salt therapy. The hypoprothrombinemia seen in some of these patients may be so severe as to give rise to brisk hemorrhage during the postoperative period.<sup>1</sup>

The cause of the postoperative prothrombin reduction seen in many patients with biliary fistula or obstructive jaundice has been subjected to controversy. In theory the postoperative hypoprothrombinemia may be the result of three factors: (1) loss of prothrombin commensurate with the amount of blood lost; (2) damage to the liver attendant on surgical procedures and anesthesia, and finally (3) failure to reestablish the body's normal reserves of prothrombin or one of its precursors.

The point of view held by most workers has been that the anesthetic agents employed were capable of producing sufficient damage to the liver to account for any fall in prothrombin which might appear during the postoperative period.<sup>2</sup> At present there are no experimental data correlating hepatic damage and hypoprothrombinemia due to anesthesia to support this thesis except cases in which chloroform was the anesthetic agent.<sup>3</sup>

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From the Department of Surgery of the University of Chicago.

This work has been aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Stewart, J. D.: Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, *Ann. Surg.* **109**:528, 1939.

2. Cullen, S. C.; Ziffen, S. E.; Gibson, R. B., and Smith, H. P.: Anesthesia and Liver Injury, with Special Reference to Plasma Prothrombin Levels, *J. A. M. A.* **115**:991 (Sept. 21) 1940.

3. Warren, R., and Rhoads, J. E.: The Hepatic Origin of the Plasma-Prothrombin Observations After Total Hepatectomy in the Dog, *Am. J. M. Sc.* **198**:193, 1939.

Lord<sup>4</sup> emphasized the factor of mechanical trauma to the liver associated with surgical procedures as a possible cause of the postoperative hypoprothrombinemia, and he demonstrated that such a prothrombin reduction can be experimentally produced in dogs by massaging the liver at the time of laparotomy. Cullen and others<sup>2</sup> have confirmed this observation.

Allen and Livingstone,<sup>5</sup> in a preliminary report on studies carried out on the human being, suggested that failure to establish an adequate prothrombin reserve before operation is probably a significant factor in causing the postoperative reduction of prothrombin in these patients.

In this paper data are presented which extend and confirm our previous report.

#### PRESENTATION OF DATA

In table 1 are compiled data obtained on 97 patients who were subjected to major surgical procedures other than operations on the biliary

TABLE 1.—*Prothrombin Studies on Nonjaundiced Surgical Patients*

Number of Patients	Anesthesia	Period of Anesthesia, Min.			Prothrombin, %	
		Maximum	Minimum	Average	Pre-operative	Post-operative
26	Ethylene oxygen.....	210	15	65	100	100
20	Ether.....	300	20	75	100	100
17	Procaine hydrochloride (local)	60	15	30	100	100
16	Spinal.....	75	22	45	100	100
14	Nitrogen monoxide .	180	20	45	100	100
9	Vinethene.....	21	8	15	100	100
4	Splanchnic .....	90	55	70	100	100

tract and on 9 patients who underwent minor operations. In none of these patients was there any evidence of jaundice, poor fat absorption or disease of the liver. The anesthetic agents used are listed in the order of frequency in which each was employed in this study. Prothrombin determinations<sup>6</sup> were made in the case of each patient pre-operatively and were repeated daily for at least four days during the postoperative period. In only 1 case was a reduction in prothrombin observed. In this case two surgical procedures were carried out on consecutive days with ethylene-oxygen anesthesia over a four-hour period on the first day and a three and one-half-hour period on the

4. Lord, J. W., Jr.: Effect of Trauma to the Liver on the Plasma Prothrombin, *Surgery* 6:896, 1939.

5. Allen, J. G., and Livingstone, H.: Studies on the Early Postoperative Reduction of Promthrombin in the Jaundiced and Biliary Fistula Patient, with Special Reference to Anesthesia, *Anesthesiology* 1:89, 1940.

6. Allen, J. G.; Julian, O. C., and Dragstedt, L. R.: The Use of Serial Dilution in the Determination of Prothrombin by the One-Stage Technique, *Arch. Surg.* 41:873 (Oct.) 1940.

second day. On the second day icterus associated with oliguria and hyperpyrexia developed, and the patient died on the fourth postoperative day, apparently in acute hepatic failure. Autopsy was not permitted.

Studies on loss of blood<sup>7</sup> were carried out on 11 of the patients listed in table 1 and on 1 patient from the group listed in table 3. The surgical procedure and the estimated quantity of blood lost are presented in table 2. The volumes of blood lost varied considerably, ranging from 785 to 175 cc. Again, in only 1 patient was a reduction in prothrombin observed. That patient (case 12), who suffered from numerous abscesses of the liver, had a preoperative prothrombin deficiency which did not respond to vitamin K and bile salt therapy. There was no further significant reduction in prothrombin up to the time of death from septicemia, on the second postoperative day.

TABLE 2.—*Loss of Blood and Prothrombin Studies Made on Nonjaundiced Patients Subjected to Operation*

Case	Procedure	Blood Loss, Cc.	Prothrombin, %	
			Preoperative	Postoperative
1	Hysterectomy.....	480	100	100
2	Neck dissection.....	260	100	100
3	Mastectomy.....	785	100	100
4	Cervical laminectomy.....	695	100	100
5	Lobectomy.....	475	100	100
6	Mikulicz resection.....	360	100	100
7	Sarcoma of abdominal wall.....	560	100	100
8	Combined abdominoperineal resection.....	620	100	100
9	Subtotal gastrectomy.....	375	100	100
10	Panlaryngectomy.....	475	100	100
11	Lumbar laminectomy.....	685	100	100
12	Abscess of liver.....	175	58	55

Table 3 presents data obtained on 13 patients with obstructive jaundice and on 2 patients with biliary fistula. Preoperative vitamin K therapy, with 2-methyl-1, 4-naphthoquinone and bile salts, was instituted and elevated the level of plasma prothrombin to normal in each patient before operation was performed. The daily dose of naphthoquinone and the number of days that this drug was administered preoperatively to each patient are indicated in the table. The level of plasma prothrombin was determined daily for each patient during both the preoperative and the postoperative period. To none of the patients in this group was any vitamin K administered during the postoperative period until after a definite drop in the prothrombin level appeared. If by the fourth postoperative day no reduction in prothrombin occurred and the patient was taking food by mouth and if adequate bile salts were available for intes-

7. Gatch, W. D., and Little, W. D.: Amount of Blood Lost During Some of the More Common Operations, J. A. M. A. **83**:1075 (Oct. 4) 1924.

tinal absorption, further prothrombin studies were made at irregular intervals until the tenth day, when these determinations were discontinued. In every patient any prothrombin deficiency encountered during the postoperative period responded rapidly to vitamin K and bile salt

TABLE 3.—*Data on Patients with Corrected Prothrombin Deficiency, Showing the Correlation Between the Duration of Preoperative Vitamin K Therapy and the Length of Time During the Postoperative Period Before a Reduction in Prothrombin Appeared*

Case	Diagnosis	Anesthetic	Period of Anesthesia, Min.	Prothrombin, %		Vitamin K, Mg.	Days Given	Day Prothrombin Fell
				Initial	Pre-operative			
1	Stone in common duct	Procaine hydrochloride (spinal) and ethylene-oxygen	210	45	100	8	7	7
2	Stricture of common duct	Nupercaine and ethylene-oxygen	90	15	100	8	5	5
3	Fistula of common duct	Procaine hydrochloride (spinal) and ethylene-oxygen	100	55	100	8	5	6
4	Stricture of common duct	Nupercaine and ethylene-oxygen	75	100	100	?	21	19
5	Stone in common duct	Procaine hydrochloride (spinal) and ethylene-oxygen	65	43	100	8	1	2
6	Stone in common duct	Procaine hydrochloride (spinal) and ethylene-oxygen	95	63	100	8	4	5
7	Carcinoma of pancreas	Nupercaine and nitrogen monoxide-oxygen	100	33	100	8	3	3
8	Stone in common duct	Procaine hydrochloride (spinal) and nitrogen monoxide-oxygen	110	28	100	8	5	6
9	Biliary fistula	Ethylene-oxygen	250	35	100	8	2	1
10	Stone in common duct	Procaine hydrochloride (spinal) and nitrogen monoxide-oxygen	235	100	100	8	1	1
11	Stone in common duct	Ethylene-oxygen and ether	145	66	100	8	4	4
12	Carcinoma of head of pancreas	Nupercaine (spinal)	90	28	100	8	2	1
13	Stricture of common duct	Ethylene-oxygen and ether	195	61	100	8	1	2
14	Carcinoma of head of pancreas	Ethylene-oxygen and ether	65	56	100	8	2	3
15	Stone in common duct	Nupercaine (spinal) and ethylene-oxygen	150	82	100	8	1	1

therapy, returning to normal within twenty-four hours after the administration of these compounds.

#### COMMENT

The role of the anesthetic agent employed for these patients does not appear to be a significant factor in the production of postoperative hypoprothrombinemia. The reduction was observed in patients subjected to

spinal anesthesia as well as those subjected to general anesthesia. Likewise, none of the 106 patients who underwent surgical procedures other than operations on the biliary tract gave evidence of postoperative hypoprothrombinemia except 1, who had probable acute hepatitis and died.

The question still unanswered is: Might not the already damaged liver be more susceptible than the normal liver to the potentially toxic effects of anesthesia? Recently, Allen, Kable and Livingstone<sup>8</sup> studied the effects of ether, ethylene, nitrogen monoxide, divinyl ether (vinethene) and cyclopropane administered with oxygen to dogs in which the prothrombin content of the plasma had been reduced by initial chloroform anesthesia. None of these five anesthetics, even when given on consecutive days to an animal with hypoprothrombinemia and hepatic insufficiency, produced any further reduction of prothrombin or retarded the return of hepatic function, as indicated by the return of the value for prothrombin to normal within five to seven days after the chloroform anesthesia. We have made similar studies on 3 patients with cirrhosis and prothrombin deficiency who did not respond to vitamin K therapy. In none of these patients was a further reduction in prothrombin encountered when they were subjected to operations carried out with general anesthesia. While so small a series does not permit a conclusion on this point, it suggests that even when the liver is damaged sufficiently to produce hypoprothrombinemia subsequent surgical procedures and anesthesia probably do not produce a further reduction of prothrombin.

The data in table 2 would seem to indicate that loss of blood encountered at the time of operation probably is not a major factor in the development of postoperative hypoprothrombinemia. These studies on loss of blood, carried out on 11 patients with normal channels for bile excretion and without apparent hepatic disease, revealed losses ranging from 260 to 785 cc. but showed no hypoprothrombinemia. In a previous report<sup>5</sup> we described a patient who was subjected to a subtotal gastrectomy. By the twelfth postoperative day the value for prothrombin had fallen to 28 per cent, probably as a result of repeated aspirations of contents of the upper part of the intestinal tract. Within four hours after the prothrombin level of 28 per cent was observed the patient had a massive emesis of blood. A posthemorrhagic prothrombin determination did not disclose any further reduction of the prothrombin concentration as a result of the hemorrhagic episode. Further studies on similar patients are necessary before final conclusions on the effects of loss of blood per se can be drawn.

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8. Allen, J. G.; Kable, V., and Livingstone, H.: Effects of Anesthetic Agents on Prothrombin Concentrations in Experimental Animals, *Anesth. & Analg.*, to be published.



From the data thus far discussed it would appear that neither the surgical procedure and its accompanying loss of blood nor the anesthetic agent administered, exclusive of chloroform, presents an acceptable explanation for the postoperative hypoprothrombinemia. However, the postoperative reduction of plasma prothrombin in the patient with jaundice or a biliary fistula can be accounted for on the basis of inadequate preoperative vitamin K therapy. Table 3 clearly indicates that there is a close correlation between the period during which vitamin K is administered preoperatively and the number of days before the onset of postoperative hypoprothrombinemia. The longest period before the prothrombin level declined occurred in a case of jaundice due to stricture of the common duct. In this case an unknown quantity of vitamin K with bile salts was given for three weeks before the patient entered the hospital. At operation drainage of the right hepatic duct was done, which still permitted no flow of bile into the gastrointestinal tract, and it was nineteen days before any reduction in prothrombin appeared. Likewise, those patients receiving the least amount of vitamin K therapy showed the earliest appearance of the postoperative hypoprothrombinemia. As may be seen from the data in cases 10 and 11, even when no initial reduction in plasma prothrombin appears an early reduction may rapidly occur in the absence of preoperative therapy.

The close correlation between the amount of preoperative vitamin K therapy and the period which elapsed before a postoperative reduction appeared confirms our original postulate, namely, that inadequate preoperative administration of vitamin K is the most important single factor in the production of postoperative hypoprothrombinemia. This concept would imply that the vitamin in some form or prothrombin or one of its precursors can be stored within the body. The site of storage seemingly is the liver, since a sharp reduction rapidly follows the removal of this organ in the dog.<sup>3</sup>

At present there is no experimental evidence concerning the storage of either vitamin K or prothrombin. There is, however, some evidence available from patients with external complete biliary fistulas. We have observed the prothrombin levels in the cases of 2 patients who had postoperative biliary fistulas. In 1 case (case 3, table 3), two and one-half months elapsed before a reduction in the level of plasma prothrombin was observed, while in the other (case 9, table 3) four months elapsed before hypoprothrombinemia appeared. In each the value for prothrombin returned to normal within twenty-four hours after the administration of vitamin K-bile salt therapy. As soon as a normal prothrombin level was obtained, administration of these drugs was discontinued, and in each case the prothrombin level fell within two days. These studies were repeated several times, the duration of vitamin

K-bile salt therapy being varied, and it was found that the longer the period of administration of vitamin K and bile salts, the longer the prothrombin could be maintained at normal levels after the discontinuance of these drugs. This, we believe, is presumptive evidence that either prothrombin or vitamin K can be stored within the body, but of course further studies are necessary before any final conclusion can be drawn.

#### SUMMARY

Prothrombin studies were made on 106 patients who underwent surgical procedures exclusive of operations on the biliary tract. Except in 1 case, no change was found in the prothrombin levels following these procedures when ether, vinethene, nitrogen monoxide, ethylene-oxygen, avertin with amylene hydrate, nupercaine, spinal, or local anesthesia was used.

Loss of blood encountered at operation was determined on 11 patients who underwent surgical procedures other than operations on the biliary tract. As much as 785 cc. of blood was lost without reducing the level of plasma prothrombin.

Thirteen patients with obstructive jaundice and 2 patients with bile fistulas received preoperative vitamin K therapy for correction of prothrombin deficiency; in all but 2 of these patients, however, a sharp drop in prothrombin occurred during the postoperative period despite the correction of the initial prothrombin deficiency.

The suggestion is made that some form of storage of vitamin K or prothrombin probably occurs within the body and that the failure to replenish this store in the patient with obstructive jaundice or biliary fistula probably accounts for the postoperative hypoprothrombinemia seen in such patients.

#### CONCLUSIONS

The postoperative hypoprothrombinemia seen in the patient with obstructive jaundice or biliary fistula is the result of inadequate preoperative vitamin K-bile salt therapy and not the result of the usual anesthetic agents employed, exclusive of chloroform.

Eli Lilly & Co. supplied the 2-methyl-1, 4-naphthoquinone and the bile salts used in this study. The vinethene was supplied by Merck & Co.

## CONGENITAL ELEVATION OF THE SCAPULA

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Although congenital elevation of the scapula was described in 1863 by Eulenburg,<sup>1</sup> the name of Sprengel,<sup>2</sup> who reported 4 cases in 1891 and who thought that his was the first description of the condition, commonly is given to the deformity. Sprengel's report was preceded also by an excellent description of a case, including autopsy observations and an interesting discussion of the significance of the omovertebral connection, by Willet and Walsham<sup>3</sup> in 1880. They reported a second case in 1883.<sup>4</sup> Since then the condition has attracted much attention, and many interesting papers have been written about it, notably those by Horwitz,<sup>5</sup> Grieg<sup>6</sup> and Schrock.<sup>7</sup> Apparently little remains to be added to the knowledge of the subject except development of a more satisfactory method of treating the deformity.

There can be little doubt that this is a true congenital deformity due to a defect in development of the embryo. A thorough description of the embryologic development of the upper extremity was published by Lewis<sup>8</sup> in 1902 and was summarized by Keibel and Mall<sup>9</sup> in their

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From the clinic of the New York Orthopaedic Dispensary and Hospital.

1. Eulenburg, M.: *Beitrag zur Dislocation der Scapula*, *Amtl. Ber. ü. d. Versamml. Deutsch. Naturf. u. Aerzte* (1862) **37**:291-294, 1868.

2. Sprengel: *Die angeborenen Verschiebung des Schulterblattes nach oben*, *Arch. f. klin. Chir.* **42**:545-549, 1891.

3. Willet, A., and Walsham, W. J.: *Congenital Malformation of the Spinal Column, Bony Thorax, and Left Scapular Arch*, *Med.-Chir. Tr.*, London **63**:256-301, 1880.

4. Willet, A., and Walsham, W. J.: *A Second Case of Malformation of the Left Shoulder Girdle, with Remarks on the Probable Nature of the Deformity*, *Brit. M. J.* **1**:513-514, 1883.

5. Horwitz, A. E.: *Congenital Elevation of the Scapula: Sprengel's Deformity*, *Am. J. Orthop. Surg.* **6**:260-311, 1908.

6. Grieg, D. M.: *Congenital High Scapula, with Which Is Included a Consideration of Brevicollis*, *Edinburgh M. J.* **31**:22-44, 1924.

7. Schrock, R. D.: *Congenital Elevation of the Scapula*, *J. Bone & Joint Surg.* **8**:207-215, 1926.

8. Lewis, W. H.: *The Development of the Arm in Man*, *Am. J. Anat.* **1**:145-183, 1901-1902.

9. Keibel, F., and Mall, F. P.: *Manual of Human Embryology*, Philadelphia, J. B. Lippincott Company, 1910, vol. 1.

"Manual of Human Embryology." Keith<sup>10</sup> gave a useful chronologic table of the development of various structures in the upper extremity, which was cited by Grieg. From these sources it appears that the upper limb bud develops as a mass of undifferentiated mesoderm in the cervical region during the fourth week. Early in the fifth week the condensation of the scleroblastema of the bud has extended to the distal part, and the anlagen of the scapula, humerus, radius and ulna are distinguishable. In the 11 mm. embryo the scapula is composed of precartilaginous surrounded by a dense blastema, and it lies opposite the lower four cervical and the upper one or two dorsal vertebrae. In the 14 mm. embryo the scapula is well developed and is composed mostly of cartilage. It has migrated caudalward, so that less than half of it lies above the first rib. Keith stated that the scapula begins to descend from the neck to the thorax at the ninth week and reaches its ultimate thoracic position at the beginning of the third month. These facts make it evident that the high position of the scapula in persons with this deformity is determined very early, at a time when the embryo is so small that it is inconceivable that any external pressure from an abnormal position in utero or deficient amniotic fluid could have any influence.

An interesting feature of this condition is the presence in a certain number of cases of a structure connecting the scapula and the cervical portion of the spine. Horwitz observed this in 34 cases, or 25 per cent of his series, and it was noted in 14 of the 50 cases in this study. One's interest is at once aroused in the origin and significance of this structure, which may be bony, cartilaginous or fibrous. It arises from the upper portion of the vertebral border of the scapula and is joined usually to one or more of the lower cervical spinous processes and laminae, most often the fourth to the seventh.

A very large bony mass of this sort was found in Willet and Walsham's first patient, who died and on whom they performed an autopsy. This observation excited their curiosity, and they discussed it with Parker,<sup>11</sup> who was an authority on the comparative anatomy of the shoulder girdle. The position and form of this bone at once suggested to him its identity with the suprascapular bone of some of the lower vertebrates. This occurs in the frog and in the toad as a large osseous dorsal appendage of the scapula, which is not, however, united to the vertebral column. In the thornback skate a suprascapular bone exists which is firmly united both to the vertebral column and to the

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10. Keith, A.: *Human Embryology and Morphology*, ed. 5, Baltimore, William Wood & Company, 1933.

11. Parker, W. K.: *A Monograph on the Structure and Development of the Shoulder Girdle and Sternum in the Vertebrata*, London, Robert Hardwicke, 1868.

scapula, forming a rigid pectoral girdle. In man and in the higher vertebrates the suprascapular bone is represented simply by the epiphysis at the vertebral border. This explanation of the occurrence of this

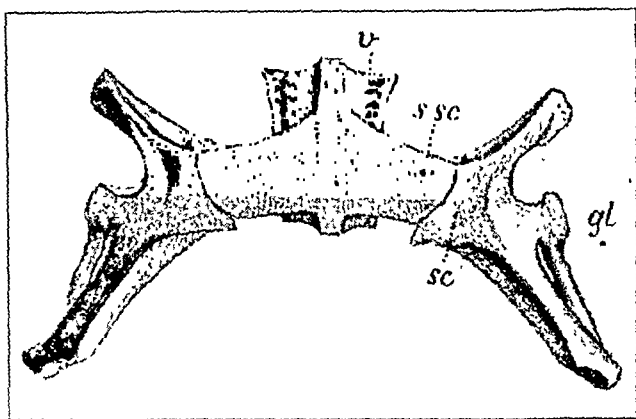


Fig. 1.—Suprascapular bone of the thornback skate, dorsal view. (From Parker.<sup>11</sup>)

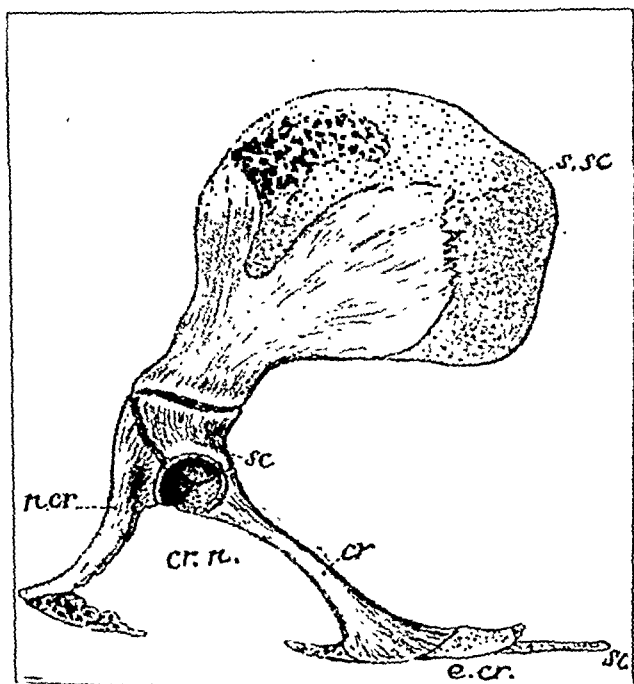


Fig. 2.—Suprascapular bone of the frog, lateral view. (From Parker.<sup>11</sup>)

unusual structure in man seems to me to be the most logical and the one most in accord with the known facts.

Fifty cases were made the basis of this study. While too few to be of real statistical value in themselves, they may be a useful addition

to those previously reported. The patients were seen at the New York Orthopaedic Dispensary and Hospital from 1912 to 1939. In some of the earlier cases the data were not as complete as could be desired. The subjects varied in age from 1 month to 31 years, and the average age at admission was 5.5 years. Twenty-seven were females and 23 were males. The deformity occurred on the right side in 23 and on the left in 20 and was bilateral in 6. It was severe in 27, moderately severe in 10, slight in 4 and not noted in 9.



Fig. 3.—Autopsy specimen in Willet and Walsham's first case. (From Willet and Walsham.<sup>3</sup>)

Associated congenital deformities of other parts of the body were present in 27 patients, which tends to confirm the thesis that high scapula is a true congenital abnormality. Of greatest frequency was the combination of malformation of the vertebrae in the cervical and upper dorsal regions, with lateral curvature of the spine and malformation and fusion of several ribs. This was found in 8 patients and was of serious import in relation to the high scapula, because the curvature in itself tended to elevate the shoulder and to interfere with attempts

to lower the position of the scapula. Malformation of vertebrae without lateral curvature was found in 4, and 6 had fusion of two or more ribs without defects in the spine. There were 6 patients with cervical ribs.

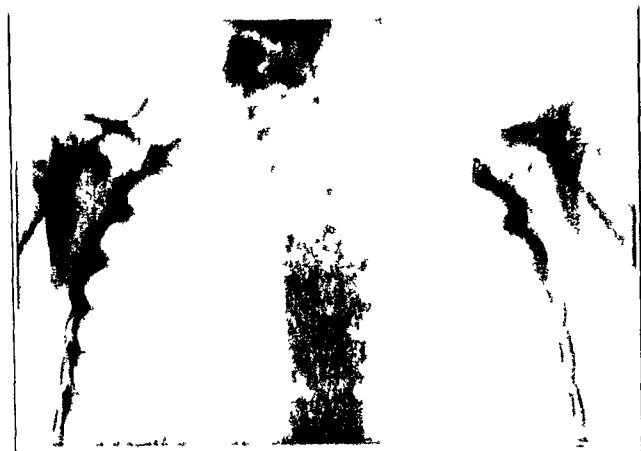


Fig. 1. Postoperative showing congenital elevation of the scapula, with an omovertebral bone.



Fig. 2. Photographs of a patient with congenital elevation of the scapula, before and after operation. (1) Pre-operative; (2) release of the scapula, as done.

The association of the last mentioned condition with congenital elevation of the scapula was explained by, first, by the theory that the normal elevation of the rib elements in the cervical region is an effect of

caudad migration of the upper extremity and the resulting pressure of the nerves as they are pulled downward. When the extremity fails to descend to its usual level, the pressure is not exerted to the same degree. Brevicollis, or short neck, was found in 1 patient and torticollis in 1. More remote congenital deformities occurred in 3 patients. No other deformity than the elevated scapula was found in 23.

Some connection between the high scapula and the spinal column was found in 14 patients, and none was noted in 36. Since this structure usually is covered by the rhomboid muscles, is difficult to palpate and in some cases is not easily demonstrated in a roentgenogram, it is quite possible that it was present but escaped detection in some of these patients. It consisted of a rhomboid osseous structure in 11 cases and of a fibrous band in 3. In the former group the bone was attached to the upper portion of the vertebral border of the scapula by cartilage in 10 and by a true joint in 1. Its connection to one or more of the lower cervical spinous processes and laminae was either by cartilage or by complete bony union. The phylogenetic significance of this structure has been discussed. Its practical importance lies in its effect in limiting the motion of the scapula and in interfering with efforts to lower it.

Of the patients in whom this point was noted, abduction of the arm was markedly limited in 17, moderately or slightly limited in 12 and not limited in 4. Of 12 patients who had an omovertebral connection the limitation of abduction was marked in 9 and moderate or slight in 3. Of 21 who had no such connection, limitation was marked in 8 and moderate, slight or absent in 13. Furthermore, the most severe grades of limitation were observed in those patients who had this structure.

Operations were performed on 14, or 28 per cent, of the 50 patients. One of the procedures was done at another hospital before the patient was admitted to this clinic. Operation was not advised for 12, was refused by 5 and is to be done subsequently on 2. In 17 cases the patient was followed for only a short time, and the question was not discussed. The operative procedures may be classed in three groups:

1. Simple removal of the omovertebral bone or fibrous band without extensive release of the scapula or any serious effort to lower it.
2. Extensive subperiosteal dissection of the scapula from its attached muscles; removal of the omovertebral bone, if present, and excision of a large portion of the scapula, including the spine and all of the bone above it, but without any attempt to anchor the bone in a lower position.
3. Extensive subperiosteal dissection of the scapula; removal of the omovertebral bone, if present; excision of only a small part of the supra-spinous portion, if any, followed by pulling the scapula down to a much lower level and suturing it to a rib.



1. Removal of an omovertebral bone was carried out successfully by Willet in 1883. It was done as the chief operative procedure in 2 cases of this series. In 2 others a fibrous band connecting the scapula with the spine was excised. In 1 of the patients, from whom an omovertebral bone was said to have been removed by another surgeon when the patient was 6 months of age, it still was present when she was examined at this clinic. In only 1 of the 4 cases in which operation was confined to removal of the bone was abduction markedly limited before operation. The result was a substantial improvement in motion. In the others the gain was slight. An omovertebral bone was removed in 3 other cases as part of a more extensive operation. In 2 of these, in which there had been marked limitation of abduction before operation, there was a subsequent increase in this range.

2. Extensive subperiosteal stripping of muscles from the scapula and removal of a large portion of the bone, including the spine and supraspinous portion, was undertaken in 4 patients. This was done in an effort to make the shoulder less conspicuous, although no attempt was made to lower the position of the remainder of the scapula. An omovertebral bone was removed in 2 of these cases. In all of the members of this group the deformity was marked. Some improvement in the upper line of the shoulder at the junction with the neck resulted in 3 cases. In the fourth there was little, if any, gain. Any cosmetic improvement was offset in 2 cases by a wide scar and in a third by marked posterior projection of the lower angle of the scapula. It was necessary to operate a second time in 2 cases, in 1 to remove a spur which grew at the superior angle and in another to excise a fibrous band which developed at the site of an omovertebral bone. Abduction was increased in 2 patients in whom it was markedly limited before operation. It is fair to state that 1 case was made difficult by a lateral curvature due to malformation of the spine.

3. Freeing of the scapula from its muscles by subperiosteal dissection and anchoring it at a lower level by suturing it to a rib, was practiced in 5 patients, of whom 4 had severe and 1 moderately severe deformity. This is essentially the operation described by Schrock and Robertson. In 1 case the supraspinous part of the scapula was cut off, and in another an omovertebral bone was removed. No bone was excised in the remaining 3. In the first patient of this group the scapula had returned to its original position at the end of two and one-half years, and there was no improvement in abduction. The release of the scapula at the time of operation probably was insufficient. In a second case, much of the correction had been lost four years later, and there was marked winging of the scapula when the arm was pushed forward. The scar was conspicuous. In a third case the patient showed excellent maintenance of correction and marked improvement in appearance at the end

of four years. One of these patients exhibited complete paralysis of the extremity after operation. This was thought to be due to excessive traction on the brachial plexus in the presence of a hemivertebra with a lateral curve and fused ribs. Four years later the paralysis had been completely recovered from except for slight weakness of the serratus anterior muscle. A large degree of correction of the deformity had been retained, and abduction of the shoulder had increased from 120 to 160 degrees. The last patient had lost part of the correction at the end of seven months but still was improved. Some calcification had occurred in the bed of the omovertebral bone, but this had not become reattached to the spine.

#### SUMMARY

The embryologic development of the scapula and upper extremity and the significance of the omovertebral bone in terms of comparative anatomy are discussed.

The physical findings in 50 cases of congenital high scapula, including associated deformities, are given.

The results of 13 operations of various types for congenital elevation of the scapula are described. An increase in abduction of the shoulder was obtained in 3 cases by removal of an omovertebral bone. Attempts to improve the appearance of the shoulder by resection of a large portion of the scapula were disappointing. In 3 of 5 cases radical freeing of the scapula and suturing it to one of the lower ribs resulted in cosmetic and functional improvement.

#### CONCLUSIONS

1. Congenital elevation of the scapula is the result of a true defect in the embryo. The omovertebral structure which occurs in about 25 per cent of these cases is a homologue of the suprascapular bone which is found in several of the lower vertebrates.

2. In many cases of congenital elevation of the scapula the cosmetic and functional defects are not of sufficient severity to warrant any operation.

3. In cases in which an omovertebral bone is associated with marked limitation of abduction at the shoulder, improvement in function may be obtained by removal of the bone.

4. In certain cases of marked elevation of the scapula, improvement in appearance and function may be had by extensive subperiosteal release of the scapula and retaining the bone in a lower position by suturing it to a rib. The operation is fraught with difficulty, however, and the result may be impaired by several complications.<sup>12</sup>

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12. D. E. Robertson, in a personal communication, reported that one of his patients had paralysis of the brachial plexus following operation, from which there was complete recovery.

# FRACTURES AND DISLOCATIONS OF THE CERVICAL PORTION OF THE SPINE

WITH A REVIEW OF EIGHTY-NINE CASES

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The cases studied were 17 from private practice and 72 from the orthopedic and neurologic services of the Los Angeles County Hospital. For statistical purposes they are regarded as one series.

## INCIDENCE

Estimating the number of patients with fractures who passed through the orthopedic services at 14,000 (a conservative figure) in three years, the 72 patients with fracture-dislocation of the cervical portion of the spine admitted in the same three year period made only 0.5 per cent of the total.

The majority (50.5 per cent) of the patients were in the age group from 20 to 39, and 79.7 per cent of them were men. The youngest was a baby of 7 months who had a fall on the head followed by paralysis and death; autopsy showed subluxation of the atlas. The oldest was a man of 72 who recovered from an automobile accident in which he sustained a dislocation of the sixth cervical vertebra anterior to the seventh.

This may be compared with an incidence of 82.5 per cent men in Soto-Hall and Haldeman's<sup>1</sup> series of 40 cases and 79.7 per cent men in a series of 79 cases collected from the general literature. Patients from 20 to 39 years of age made up 40 per cent and 43 per cent respectively of these two series.

## CAUSE

A great variety of trauma contributes to the causation of these lesions. Dislocation alone may occur with very slight trauma or none at all, as is evidenced by many cases of subluxation resulting from inflammatory weakening of muscles and ligaments of the cervical region, notably of the first and second vertebrae (Brookes and Ewerhardt;<sup>2</sup>

1. Soto-Hall, R., and Haldeman, K. O.: Bilateral Dislocation of Cervical Spine, California & West. Med. **45**:238, 1936.

2. Brookes, T. P., and Ewerhardt, F. H.: Reducing and Treating Cervical Dislocation, Arch. Phys. Therapy **13**:463, 1932.

Hess, Bronstein and Ableson;<sup>3</sup> Frank<sup>4</sup>). Congenital anomalies of the vertebrae, such as absence of the odontoid process (Roberts<sup>5</sup>), may constitute a predilection to dislocation. Mechanisms producing slight trauma, such as sneezing, coughing or sudden twisting of the head, are listed under muscular violence.

Several cases have been reported in which dislocation was found after manipulation by an osteopath or a chiropractor (Blaine;<sup>6</sup> Jacobs;<sup>7</sup> Brookes<sup>8</sup>). None of this type was found in this series.

TABLE 1.—Incidence

Sex:	
Male	79%
Female	21%
Age:	
Under 10	3.5%
10 to 19	10.5%
20 to 29	29.4%
30 to 39	21.1%
40 to 49	11.1%
50 to 59	11.7%
60 to 69	5.8%
70 up	3.3%

TABLE 2.—Cause

Motor vehicles.....	57.9%
Fall.....	23.8%
Fighting, wrestling..	6.8%
Dive.....	3.4%
Blow.....	1.1%
Muscular violence....	1.1%
Not stated.....	5.7%

As for all other fractures, accidents with motor vehicles were responsible for the majority (59.7 per cent) of the fractures in this series.

3. Hess, J. H.; Bronstein, I. P., and Ableson, S. M.: Atlanto-Axial Dislocation Unassociated with Trauma and Secondary to Inflammatory Foci in the Neck, *Am. J. Dis. Child.* **49**:1137 (May) 1935.

4. Frank, I.: Spontaneous (Non-Traumatic) Atlanto-Axial Subluxation, *Ann. Otol., Rhin. & Laryng.* **45**:405, 1936.

5. Roberts, S. M.: Congenital Absence of the Odontoid Process, Resulting in the Dislocation of the Atlas on the Axis, *J. Bone & Joint Surg.* **15**:988, 1933.

6. Blaine, E. S.: Manipulative (Chiropractic) Dislocations of the Atlas, *J. A. M. A.* **85**:1356 (Oct. 31) 1925.

7. Jacobs, C. M.: Atlas and Axis Luxation, *Am. J. Orthop. Surg.* **16**:357, 1918.

8. Brookes, T. P.: Dislocation of Cervical Spine, *J. Missouri M. A.* **27**:579, 1930.

## SYMPTOMS AND FINDINGS

The patient with the neck hyperflexed and the chin down on the chest probably has a bilateral dislocation. If the head is tilted to one side and rotated to the opposite side, there is usually a unilateral dislocation. Fracture alone, except perhaps extreme compression of two or more vertebral bodies, may not produce any visible deformity. Pain is not a prominent symptom, but tenderness on motion of the head and neck is pronounced. Difficulty in opening the mouth is suggestive of rotary dislocation of the atlas.

Neural symptoms may vary from slight tingling in the fingers to complete motor and sensory paralysis from the shoulders down. Loss of the sense of pain in the great toe is a sign of complete lesion of the spinal cord, since the fibers which convey this sensation go up the center of the cord (Stuck<sup>9</sup>). Fever, respiratory difficulty and priapism may all be present in cases of high lesions with damage to the cord.

TABLE 3.—Symptoms

	Paralysis 26.1%	Anesthesia 21.5%	Unconsciousness 35.2%
I —————	13%	5%	12.9%
II .....			19.3%
III .....			3.2%
IV —————	13%	10.5%	12.9%
V —————	39.1%	52.6%	16.1%
VI —————	31.8%	31.6%	29.7%
VII .....			0.5%

A dislocation at the fourth cervical vertebra or above, with involvement of the cord, may produce paralysis of all four extremities; if the lesion is at the level of the fifth cervical vertebra the upper parts of the arms may be spared; if it is at the level of the sixth cervical vertebra only the legs can be paralyzed. If sensation persists, motor function may return (Crutchfield<sup>10</sup>). Spasticity and increased reflexes are promising signs when present at first (Voris<sup>11</sup>).

In Roberts'<sup>12</sup> series, symptoms of compression of the cord were present with 75 per cent of the fractures and with only 10.5 per cent of the dislocations. In my series, 26.1 per cent of the patients were

9. Stuck, R. M.: Spinal Cord Compression Injuries, Broken Necks and Broken Backs, with Spinal Cord and Spinal Nerve Injury, *J. Kansas M. Soc.* **40**: 48, 1939.

10. Crutchfield, W. G.: Fracture-Dislocation of Cervical Spine, *Am. J. Surg.* **38**:592, 1937.

11. Voris, H. C.: Treatment of Fracture and Dislocation of Cervical Spine, *S. Clin. North America* **17**:543, 1937.

12. Roberts, S. M.: Fracture and Dislocation of Cervical Spine, *J. Bone & Joint Surg.* **19**:477, 1937.

paralyzed. Dislocation alone produced the paralyzes in 8 instances, fracture alone in 5 and fracture-dislocation in 10. The site of the lesion as shown in the roentgenogram did not always correspond to the site of the lesion in the cord as shown by the neurologic findings. For example, in 4 cases in which the osseous lesion was at the level of the sixth cervical vertebra there was, nevertheless, complete paralysis of all four extremities. This may be explained by assuming that the lesion of the cord extended upward from the osseous lesion or that there was another lesion of the cord at a higher level.

Analysis of the cases of paralysis showed that in 13 it was complete, of all limbs; in 5, of the legs only; in 1, of the arms only; in 2, of one arm; in 2, hemiplegia, and in 1, of the Brown-Séquard type. Except in 3 cases of dislocation of the first cervical vertebra all the paralyzes were caused by lesions of the fourth, the fifth or the sixth cervical vertebra, the injuries being about equally divided among dislocations, fractures and fracture-dislocations. Table 3 shows that there was no paralysis or sensory disturbance from lesions at the level of the second or of the third cervical vertebra. This is explained by the fact that at the level of the second and the third cervical vertebra the bony canal is larger in proportion to the size of the cord than it is at the lower cervical levels.

Loss of sensation was noted in a smaller percentage (21.5 per cent) of the cases than was loss of motion. In 35.2 per cent of the series unconsciousness immediately followed the accident and lasted from a few minutes to a few hours.

The dislocations were all anterior except 1; that is, the superior vertebra was anterior to the adjacent one below it. Considering the structure of the vertebra, it is obvious that a posterior dislocation, unless complicated by fracture, could not persist long enough to be demonstrated by roentgen examination. An anterior dislocation persists only if the superior vertebra overrides the inferior vertebra far enough so that the articular facets lock. In a few instances, especially in rotary dislocations of the first cervical vertebra over the second, the inferior facet of the upper vertebra may catch on top of the superior facet of the lower, but usually with these subluxations there is spontaneous reduction. This probably accounts for the cases in which severe neurologic symptoms occur without demonstrable lesions of bone.

In the 1 case of posterior dislocation in this series, there was a fracture of the anterior part of the body of the fifth cervical vertebra with a posterior displacement of the posterior part of the body, enough to impinge on the cord. Complete paralysis below the waistline and death in three days resulted.

## SITE OF LESIONS

The sixth cervical vertebra was involved in more cases than any other, and in 49.4 per cent the lesion was in either the fifth or the sixth cervical vertebra. This disagrees with the statement in some textbooks that the third cervical vertebra is the weakest part of the cervical portion of the spine. There was no case of isolated fracture of the atlas, but there were 6 of dislocation and 5 of fracture-dislocation of this vertebra. According to del Rosso,<sup>13</sup> isolated fracture of the atlas is very rare; a fracture of the skull and/or a fracture of the axis is usually present also. No compression fracture of the body of a vertebra was found

TABLE 4.—Site of Lesions

I	11%
II	12%
III	4%
IV	13%
V	20%
VI	29%
VII	7%
Unknown	4%

TABLE 5.—Site of Classified Lesions

	Fractures 43%	Dislocations 31%	Fractures and Dislocations 22%
I	.....	19.3%	22.7%
II	18.6%	3.2%	13.6%
III	1.6%	3.2%	4.5%
IV	13.9%	22.6%	
V	20.9%	19.3%	22.7%
VI	27.9	29%	36.4%
VII	13.9%	3.2%	

above the fifth cervical vertebra. Dislocations alone were found to be more frequent (22.5 per cent) in the first two cervical vertebrae than fracture alone (18.6 per cent). Combined fracture and dislocation involved these two in 36.3 per cent. In Soto-Hall and Haldeman's<sup>1</sup> series 55 per cent of the lesions were in the fifth and sixth cervical vertebrae. In Brookes's<sup>14</sup> series of 90 cases of dislocation alone, 57.7 per cent of the lesions were located at the level of the first and second cervical vertebrae. Blasius<sup>15</sup> (84 cases) found the fifth and sixth involved in 52.3 per cent.

13. del Rosso, L. M.: Sopra due casi di frattura "isolata" dell'atlante, Chir. d. org. di movimento 17:325, 1932.

14. Brookes, T. P.: Fracture and Dislocation of Cervical Spine, J. A. M. A. 109:6 (July 3) 1937.

15. Blasius, cited by Warshaw, D.: Dislocation of Cervical Spine: Case of Complete Forward Dislocation of VI C with Reduction by forcible Traction and Full Recovery, Ann. Surg. 99:470, 1934.

As is noted in table 6, the body of the vertebra was the part most frequently involved in fractures. This is the easiest part to demonstrate by roentgen examination, while the laminae and the pedicles may sometimes escape detection. This may in part account for the 4 per cent "unknown" in table 3. The other excuse for these unknown sites is that the patient had all the clinical symptoms of a lesion of the cervical part of the spine but died in shock before roentgen examination could be made.

#### TREATMENT

In 37.5 per cent of this series the only treatment was extension of the head followed by use of an ambulatory cast or a brace. Manipulation followed by application of a cast was done in 6.8 per cent, and a cast only was used in 15.9 per cent. Skeletal traction was applied in 5.7 per cent. In a number of cases, 17 per cent, the treatment was expectant, meaning usually that the patient was in such a serious con-

TABLE 6.—*Parts Involved in Fractures*

Body of vertebra.....	51.5%
Spinous process.....	21.2%
Odontoid process.....	13.6%
Lateral mass.....	6.1%
Pedicle.....	3%
Lamina.....	3%
Articular process.....	1.5%

dition that not much could be done to the local lesion. Another 17 per cent must be recorded under "treatment not known," owing to deficiency in the hospital records.

Reduction of dislocations may be accomplished in many cases by extension alone. However, in cases of severe or complete paralysis an attempt should be made as early as possible to reduce the dislocations by manipulation. There may be cases of immediate and complete paralysis due not to destruction of the cord but to compression by a wide dislocation. If this compression is allowed to persist for several hours, irreparable destruction of the cord may follow, with the result that the patient is more or less a cripple for life. Given a patient with complete and immediate paralysis, skilful manipulation and manual extension at once at the scene of the accident may relieve pressure and preclude permanent paralysis. No time should be consumed with a trip to an emergency hospital, a transfer to a general hospital and then a wait for roentgen examination. In view of the foregoing statistics, if there is paralysis the chances are that the lesion is at the fourth cervical vertebra or below, and one does not take much risk of respiratory



failure or other fatal result in manipulating a spine with a lesion at this level and keeping the neck in extension from the start. An emergency temporary head halter can be made out of a 3 inch (7.5 cm.) muslin bandage and two safety pins, and with this halter an ambulance man can hold the head in extension on the way to the hospital. Once in bed at the hospital, the patient should not be moved, but roentgenograms should be taken with a portable machine. One patient who walked after falling on his head and who had a gradual development of paralysis the next day died while he was being moved to have a roentgenogram taken. In another case, a boy of 15 twisted his neck in a fall in a gymnasium



Fig. 1.—*A*, roentgenogram showing dislocation of the fifth over the sixth cervical vertebra in a man aged 24. Successful reduction was accomplished by manipulation. Dislocation recurred in three months. The final condition was as shown. There were no symptoms. *B*, roentgenogram of a patient with complete paralysis and anesthesia from the neck down following a fall on the head. There was a slight fracture of the fourth cervical vertebra but no roentgen evidence of pressure on the cord.

and became unconscious. He "came to" in a few minutes and was allowed to walk to the dressing room, where he became unconscious again. He was then taken to a hospital and put to bed, where after gentle manipulation he became conscious again. Roentgen examination after the manipulation gave negative results.

The Walton<sup>16</sup> manipulation was used more frequently than the Taylor<sup>17</sup> method in this series. Reduction of the dislocation is a procedure which requires more skill than force, and by the former method delicate control can be maintained. The forcible extension which is the essence of the Taylor method may be necessary for some bilateral lesions. Walton devised his method in the pre-roentgen-ray days and based his plan on observations at the autopsy table. He called it retro-lateral flexion without extension. He held that forcible extension is not only unnecessary but actually may hinder reduction by preventing action of the fulcrum mechanism on the opposite side while one side is being reduced.

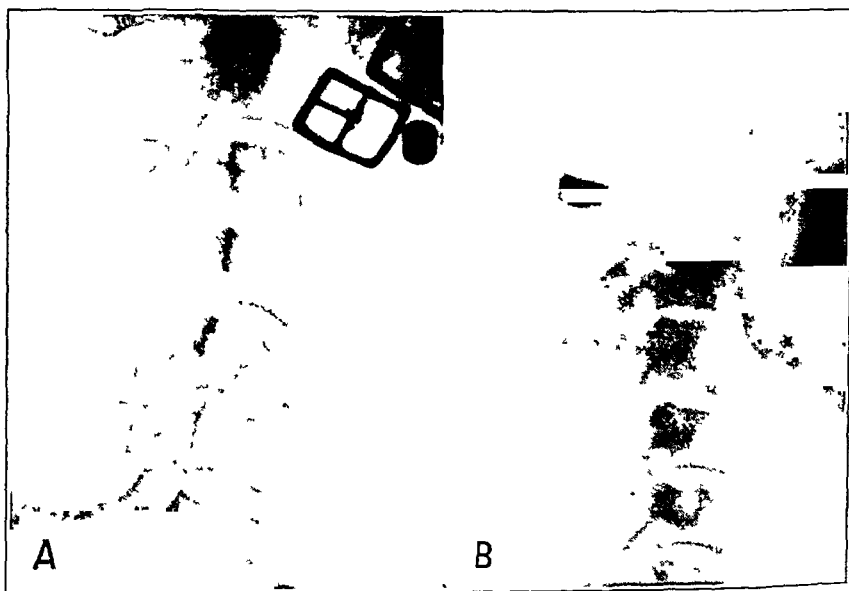


Fig. 2.—*A*, roentgenogram of a man aged 44. His was the only case of posterior dislocation in the series. The lesion was not a true dislocation at the joint but a displacement of a fragment of the body of the fifth cervical vertebra. Paralysis and anesthesia were present below the waist. Death occurred in three days. *B*, roentgenogram showing a fracture of the second cervical vertebra, involving the odontoid process, in a man aged 24. There was no paralysis or anesthesia. The patient collapsed during application of skeletal traction and died nine hours later.

No open reductions, fusions or laminectomies were done in this series, although some such procedure might have been indicated in at least 2 cases. In 1 of these there was a recurrence of dislocation of the

16. Walton, G. L.: Further Observation on Cervical Dislocation and Its Reduction, *Boston M. & S J.* **149**:445, 1903.

17. Taylor, A. S.: Fracture-Dislocation of Cervical Spine, *Ann Surg* **90**:321, 1929.

fifth cervical vertebra about two months after a successful reduction by manipulation. In the other, the patient removed his plaster collar himself and at once had a recurrence of a dislocation of the fourth cervical vertebra. Voris<sup>11</sup> stated that manipulation with the patient under anesthesia probably gives a higher mortality than laminectomy. However, in our series there was no death which could be attributed to manipulation alone, with or without anesthesia.

In a few cases manipulation was unsuccessful, and dislocation without paralysis persisted. In 1 case the patient was not seen until five weeks after the accident. Since there were no neural symptoms, a dislocation of the sixth cervical vertebra was allowed to persist because the patient refused to submit to manipulation, wishing to let well enough alone. At present, eight years later, he takes long mountain hikes and other strenuous exercise in spite of evident torticollis resulting from the persisting dislocation.

The application of skeletal traction is delegated to the brain surgeons. The Crutchfield tongs is the apparatus of choice for this. Crutchfield<sup>10</sup> gave credit to Coleman as the first to use skeletal traction on the skull in 1932. Cone and Turner<sup>18</sup> at a meeting of the American Orthopedic Association in Toronto, Canada, in July 1932, reported several cases in which they had used skeletal traction by means of wires through drill holes in the skull. Later they reported 12 cases of fusion after reduction by skeletal traction, stating that dissection in this region is done with an electrocautery to avoid trauma. Crutchfield<sup>19</sup> reported 42 cases of treatment with skeletal traction up to 25 pounds (11.3 Kg.). In all 27 cases in which he treated the injury within two months complete reduction was obtained. One advantage of the Crutchfield tongs is that the patient can be turned on the side easily without disrupting the extension apparatus.

Wiring of the spinous processes to prevent recurrence of dislocation has been done by Ryerson and Christopher,<sup>20</sup> Cotton,<sup>21</sup> Lane,<sup>22</sup> Speed,<sup>23</sup> Osgood<sup>24</sup> and others, with varying success. The difficulty with this

18. Cone, W., and Turner, W. G.: The Treatment of Fracture-Dislocation of the Cervical Vertebrae by Skeletal Traction and Fusion, *J. Bone & Joint Surg.* 19:584, 1937.

19. Crutchfield, W. G.: Treatment of Injuries of the Cervical Spine, *J. Bone & Joint Surg.* 20:696, 1938.

20. Ryerson, E. W., and Christopher, F.: Fracture of Cervical Vertebrae: Operative Correction, *J. A. M. A.* 108:468 (Feb. 6) 1937.

21. Cotton, cited by Ryerson and Christopher.<sup>20</sup>

22. Lane, cited by Ryerson and Christopher.<sup>20</sup>

23. Speed, cited by Ryerson and Christopher.<sup>20</sup>

24. Osgood, cited by Ryerson and Christopher.<sup>20</sup>

method seems to be that the bone of the spinous processes is not dense enough to stand the strain, and the wire pulls out.

Dislocations of the upper cervical vertebrae require long-continued immobilization, with support of the head to insure against recurrence and a fatal result. Osgood and Lund,<sup>25</sup> reporting fractures of the odontoid process, advised immobilization for six months and stated that manipulation is dangerous in these cases. They called attention to the fact that the odontoid process is stronger than the anterior arch

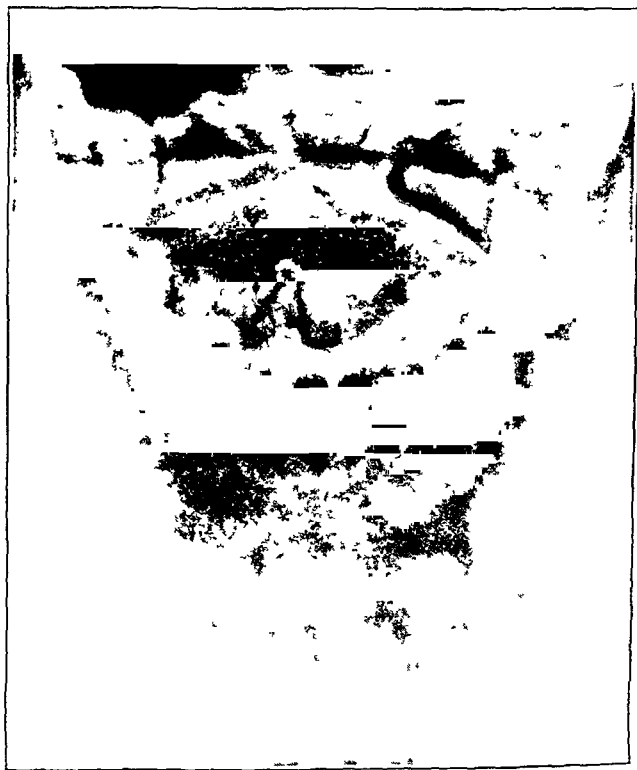


Fig. 3.—Roentgenogram of a boy aged 17. There were symptoms of dislocation of the upper part of the cervical portion of the spine. A developmental anomaly was present; there was failure of the odontoid process to fuse with the second cervical vertebra. The symptoms subsided after a week in extension.

of the atlas but weaker than the articular ligament which encircles the odontoid process posteriorly. Jefferson,<sup>26</sup> in a report of 4 cases of fracture of the atlas, stated that if this condition is not recognized and reduced it may cause death due to a sudden increase of dislocation of the fragments. Open reduction may be necessary for this fracture.

25. Osgood, R. B., and Lund, C. C. · Fractures of the Odontoid Process, *New England J. Med.* 198:61, 1928

26. Jefferson, G.: On Fractures of the First Cervical Vertebra, *Brit. M. J.* 2:153, 1927.

Hudson<sup>27</sup> found that conservative extension methods without operation were successful in 45 cases which he reported. King<sup>28</sup> advised skeletal traction if anesthesia and paralysis are present. Oppel<sup>29</sup> removed an entire anterior arch of a fractured atlas and obtained improvement of symptoms. Bonnet<sup>30</sup> advised postponing fusion operations for two or three months to avoid operative accidents. He stated that he uses local anesthetics. Pybus<sup>31</sup> successfully reduced an anterior dislocation of the fifth cervical vertebra by open operation and direct leverage, approaching the anterior aspect of the spine by lateral incision and postpharyngeal dissection. Craig<sup>32</sup> removed the posterior arch of the first cervical vertebra and the posterior margin of the foramen magnum with the region under local anesthesia to relieve gradually developing compression myelitis. The patient recovered to normal. Spinal fusion was done in all of 18 cases of fracture-dislocation of the lower cervical vertebrae reported by Cole.<sup>33</sup> Langworthy<sup>34</sup> reported 30 cases of dislocation, in 13 unilateral and in 17 bilateral, in all of which the dislocations were reduced by the Walton method, mostly with the patient under general anesthesia. Casts were applied at once with the spine in hyperextension.

#### RESULTS

The general mortality of the entire series was 25.8 per cent. Of the 23 patients who died, 15, or 65.2 per cent, had lesions of the fifth and/or the sixth cervical vertebra. Table 1 shows that 49 per cent of the lesions were of the fifth and/or the sixth cervical vertebra, so that the mortality from involvement of these two vertebrae is greater than that noted for any of the others. Only 20 per cent of the patients with lesions of the first and/or the second cervical vertebra died. Most of the deaths, 73.9 per cent, occurred in the first five days; 39.1 per cent, in the first twenty-four hours.

27. Hudson, O. C.: Fractures and Dislocations of the Cervical Spine, *J. Bone & Joint Surg.* **17**:324, 1935.

28. King, T.: Some Difficulties in the Treatment of Dislocation of the Cervical Spine, *Australian & New Zealand J. Surg.* **6**:380, 1937.

29. Oppel, W. A.: Anterior Subluxation of the Atlas, *Lancet* **1**:698, 1927.

30. Bonnet, G.: Deux observations de "dislocation atlo-axoïdienne" sans troubles bulbo-médullaires. Echec du traitement orthopédique: Verrouillage de sûreté par greffe d'Albee, *Bull. et mém. Soc. nat. de chir.* **59**:1296, 1933.

31. Pybus, F. C.: Fracture-Dislocation of the Cervical Spine and Its Open Reduction, *Brit. M. J.* **2**:860, 1936.

32. Craig, W. M.: Fracture-Dislocation of the Cervical Vertebrae Without Injury to the Spinal Cord, *S. Clin. North America* **11**:841, 1931.

33. Cole, J. P.: Dislocation and Fracture-Dislocation of the Lower Cervical Vertebrae, *Arch. Surg.* **35**:528 (Sept.) 1937.

34. Langworthy, M.: Dislocation of Cervical Spine: Thirty Cases, *J. A. M. A.* **94**:86 (Jan. 11) 1930.

As might be expected, the mortality among patients with complete paralysis was high. Of the 18 with paralysis of three or more limbs, 13 (72.2 per cent) died, all within nine days except 1 man, who lived forty-four days. One patient with complete and immediate paralysis is living after eight years, still paralyzed from the neck down. He showed only a mild compression of the sixth cervical vertebra in the roentgenogram; the damage to the cord may have been caused by a dislocation which reduced itself spontaneously. The neurologic consultant advised against operation on the ground that the cord was beyond repair. Another man totally and immediately paralyzed by a fall on the head and shoulders is living after three years. A bilateral dislocation was reduced within three hours by the Walton method with the patient under general anesthesia. On coming out of the anesthetic he could move his hands and made further improvement under weight extension. He is now spastic, walks a little with help, feeds himself, has fair biceps but no triceps power and has trouble with the bladder.

Manipulation was successful in 55.5 per cent of the cases in which it was tried. In 22.2 per cent the position was improved, and in 22.2 per cent manipulation failed to reduce the dislocation. There was recurrence of the dislocation after good reduction in 3.3 per cent.

In fractures, there was never much change in the position of the fragments after extension. In 1 case the displaced body of the second cervical vertebra could be felt with the fingers through the mouth, but it did not yield to gentle pressure combined with extension of the head; neither did it show any change after five weeks under traction with Crutchfield's tongs. The patient still wears a support after nine months and has never had any neurologic symptoms.

Crutchfield<sup>19</sup> reported that 80 per cent of patients with hopeless lesions of the cord died within ten days. The mortality in 45 cases reported by Hudson<sup>27</sup> was 13.3 per cent. Roberts<sup>35</sup> reported 21 cases, with 19 per cent mortality. It is interesting to note that in the pre-roentgen days the mortality records were much higher, 77 per cent (Ashhurst<sup>36</sup>) and 92.6 per cent (Blasius<sup>37</sup>), the explanation being that only the serious lesions were recognized. For the atlas alone, Jefferson<sup>38</sup> reported a mortality rate of 54 per cent, and for fracture of the odontoid process Osgood and Lund<sup>25</sup> reported 50 per cent mortality. In a total of 59 cases from the literature, the mortality was 10.1 per cent.

35. Roberts, S. M.: Dislocation of Cervical Spine, *J. Bone & Joint Surg.* 19: 199, 1937.

36. Ashhurst, cited by Cole.<sup>33</sup>

37. Blasius, cited by Cole.<sup>33</sup>

38. Jefferson, G.: Fractures of the Atlas Vertebra, *Brit. J. Surg.* 7:407, 1920.

#### CONCLUSIONS

The study of these cases suggests that in some instances severe and permanent paralysis might have been avoided if a reduction of the dislocation could have been done earlier. Perhaps one should do more laminectomies for lesions which are usually considered hopeless. When complete paralysis exists but no interference with the neural canal can be demonstrated by roentgen examination, it may be that the cord is not completely severed but that edema inside the dura is causing a block which could be relieved by laminectomy and longitudinal incision of the dura. The patient has nothing to lose and everything to gain from operation.

# VERTEBRAL COMPRESSION FRACTURES SUSTAINED DURING CONVULSIONS

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It is well known that muscular action alone can break bones, such as the femoral neck<sup>1</sup> or the bones of the forearm.<sup>2</sup> However, fractures of vertebral bodies by muscular action, except in cases of tetanus, were practically unknown until recently, after the advent of convulsive shock therapy, although such fractures have been reported to have occurred in breeding stallions. The question of fractures from convulsive spasms has assumed more importance since inauguration of convulsive shock therapy for the psychoses. Since the introduction of shock therapy in 1935, occasional fractures have been reported by various observers; however, many of the fractures were overlooked because of the mildness or absence of symptoms. In the early days of convulsive shock therapy, no roentgenograms were taken unless the symptoms called for the procedure; recently roentgen examination has been routinely employed by one of us (S. A.) before and after treatment in all cases of convulsive shock therapy. In this communication a report is made of 7 vertebral compression fractures sustained during convulsions induced by metrazol in a group of 30 patients. These fractures occurred in 6 men and 1 woman between the ages of 28 and 50; the condition of 6 had been diagnosed as schizophrenia, and that of 1, as manic-depressive psychosis. Each patient received between seven and twenty injections of metrazol and responded with moderate or severe convulsions. Three of the patients did not complain of any symptoms suggestive of a fracture; 3 others complained of tenderness and pain in the region involved, radiating along the spinal nerve roots, which lasted from three days to two weeks; in 1 of the patients the discomfort lasted for over a year,

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From the Spring Grove State Hospital and the Springfield State Hospital.

1. Baish: Ueber chronischen Tetanus, München. med. Wehnschr. **65**:127, 1918.  
Androp, S.: Bilateral Fracture of the Femoral Necks Caused by Metrazol Convulsions, J. Nerv. & Ment. Dis., to be published.

2. Wilhelm, T.: La cyphose tétanique, J. de chir. **22**:295, 1923.



necessitating constant wearing of a corset. In 1 of the patients the patellar reflexes became unequal, the inequality lasting about ten days. The onset was sudden, the convulsion lasting on the average one minute and passing through a succession of clonic-tonic-clonic stages. The fractures sustained resembled those seen in cases of tetanus. The anterior part of the vertebra is almost always compressed, without apparent injury to the spinal cord, and the posterior part may remain intact. Figure 1 illustrates a typical vertebral compression fracture sustained during a convulsion induced by metrazol shock therapy. A brief review of the literature and a study of the mechanism of vertebral compression fractures sustained during convulsions will be presented.



Fig. 1.—Typical vertebral compression fracture sustained during a convulsion induced by metrazol shock therapy.

#### FRACTURES IN CASES OF TETANUS

Roberg<sup>3</sup> and others have reported a limited number of cases of vertebral fractures which were demonstrated roentgenographically after tetanus. A definite description of anatomic changes induced in vertebral bodies by tetanic convulsions has been made in only 3 cases.

#### FRACTURES IN CASES OF EPILEPSY AND OTHER CONVULSIVE DISORDERS

Although one would strongly suspect the occurrence of vertebral fractures due to muscular spasm during epileptic attacks, there is a

3. Roberg, O. T., Jr.: Spinal Deformity Following Tetanus and Its Relation to Juvenile Kyphosis, *J. Bone & Joint Surg* **35**:603, 1937.

paucity of cases reported in the literature. Ziskind and Ziskind<sup>4</sup> reported 3 cases of fracture of the spine occurring during epileptic attacks and cited 3 other cases, reported by Rand. As we could find no other cases in the literature, it was deemed of much interest to examine the spines of a series of epileptic patients to see whether any of them showed vertebral fractures. A group of 50 patients from an epileptic colony with frequent severe grand mal seizures were selected, and their vertebral columns were roentgenographed anteroposteriorly and laterally. No sign of a vertebral fracture was observed in any of these patients. In a similar manner, several groups of patients suffering from convulsions on a syphilitic or an arteriosclerotic basis or due to cerebral neoplasms were examined and were found roentgenographically free from any signs of fractures in the vertebral column. No cases of vertebral fracture due to strychnine-induced convulsions or to eclampsia were found in the literature. From a review of the literature one is convinced that compression fractures of the vertebral column are by far more frequent with convulsive shock therapy than with any of the convulsive disorders. These fractures seldom occur in epileptic seizures or the other convulsive disorders, because the tonic stage is not as long and violent as in the attacks due to metrazol; the injury occurs during the tonic stage.

#### LOCATION OF FRACTURES

In convulsions due to shock therapy the fractures occur most frequently in the area from the fourth to the eighth thoracic vertebra, which is the region least covered by the spinal erector muscles and least resistant to a contraction of the musculature of the anterior part of the trunk. In cases of tetanus, fractures occur almost entirely in the region of the fourth to the sixth thoracic vertebra; only 2 occurred in the lumbar region. The very few reported as occurring in cases of epilepsy occurred in the tenth, eleventh and twelfth thoracic and in the second and third lumbar vertebrae. Ordinary compression fractures occur in the twelfth thoracic, the first lumbar and the fifth, sixth and seventh cervical vertebrae. According to Fick,<sup>5</sup> the fifth thoracic vertebra is the weakest in the entire spine.

#### SYMPTOMS OF FRACTURES

The usual symptoms indicating that fractures of the vertebrae have taken place are tenderness and pain of the affected area of the spine, radiating from the spinous processes along the spinal nerve roots. This

4. Ziskind, E., and Somerfeld-Ziskind, E.: *Compression Fracture of the Spine in Epilepsy*, Bull. Los Angeles Neurol. Soc. 4:45, 1939.

5. Fick, R.: *Handbuch der Anatomie und Mechanik der Gelenke unter Berücksichtigung der bewegender Muskeln*, Jena, Gustav Fischer, 1911, vol. 3.

as a rule will disappear within a few days or a week. One of our male patients was compelled to wear a corset for over a year; another patient showed inequality in his patellar reflexes lasting only ten days.

#### POSSIBLE CAUSES OF FRACTURES

Restraint was mentioned by Palmer<sup>6</sup> as a predisposing cause of fractures; however, it was eliminated as a possible factor in our series. The patients were allowed perfect freedom of movement during the convulsions, with no interference from the nursing personnel. The treatments were administered in bed, and the patients were carefully guarded against a direct injury to the spine. The contributory effect of local circulatory disturbance should be considered, as should hypocalcemia, which first takes place in the bones of the vertebral column, which is most labile. Moffat<sup>7</sup> pointed out that pathologic fractures of the vertebrae resulting from loss of calcium from the spinal column are not uncommon and are, in the majority of cases, due to a faulty diet. He reported 10 cases. Although no determination of calcium balance was made in the group of cases of fractures due to metrazol therapy, there was nothing to suggest a background of disease or defect in the muscular system or in the skeleton. Although many still question the possibility of this occurrence in normal vertebral bodies, it has been generally impossible to find a predisposing condition. The age of the patient, apparently, is not a factor in this condition.

#### SEVERITY OF FRACTURES

All degrees of severity, from a severe crush to the slightest chip off the anterior rim or a small crack, are encountered. The type most frequently encountered with metrazol shock therapy is that due to compression of the anterior part of the vertebra, with or without involvement of the posterior part. The vertebral bodies are cancellous, with a rich blood supply; evidently compression fractures are accompanied by extravasation of the contents of the disk, with a consequent lessening of its height. This will be confirmed when the material comes to pathologic study. Roberg<sup>3</sup> claimed that roentgen determination of a fracture is not absolutely certain. Fragmentation of the bony structure extending through the periphery of the shadow is certain evidence of fracture. Displacement of one portion of the body against another body in a sagittal or a frontal direction also demonstrates a fracture. Flattening in a vertical direction or isolated wedge formation

6. Palmer, H. A.: Vertebral Fractures Complicating Convulsion Therapy, *Lancet* **2**:181-183, 1939.

7. Moffat, B. W.: Pathologic Fractures of the Spine Associated with Disorders of Calcium Metabolism, *Arch. Surg.* **28**:603 (June) 1934.

associated with a continuous line of increased density in the interior of the body, even in the presence of an intact outline, is suggestive of a break in the spongiosa. It is plausible that only a microscopic fracture may be present.

#### MECHANISM OF FRACTURES

Although the mechanism of fractures occurring during convulsions or muscular spasms is still not definitely established, it may be explained on the basis of the contraction of certain muscle groups during the convulsions. The typical postconvulsive shock therapy fracture of the thoracic vertebrae is caused by a predominating, severe contraction of the anterior musculature of the trunk, which produces antelexion of the spine at this point. Radmann<sup>8</sup> explains the mechanism of spinal compression fractures as the result of muscular action incited by external trauma. Accordingly, the force of a jarring or bending fracture of the spine is not transmitted simply in a vertical direction from one body to another, but its horizontal and vertical components are resisted by a third component, represented by a sudden tension occurring in muscles fixed at a point anterior to the spine and contracting reflexly. The contraction of these muscles compresses the anterior surfaces of the bodies in a mechanism similar to that of tetanic curving of the thoracic portion of the spine anteriorly.

#### FORCE INVOLVED

The muscular contraction which causes a vertebral compression fracture is a force that cannot be estimated; it is not known what resistance a vertebral body makes to such a force, and the leverage which is transmitted by the ribs and in the bending of the spine on itself has not yet been measured. That the muscular contraction in convulsions due to metrazol shock therapy is of extreme severity is illustrated in figure 2, which shows a bilateral fracture of the femoral necks. This occurred at the height of the tonic stage, when a distinct snap was heard. Göcke<sup>9</sup> found that weights up to 480 Kg. did not alter the form of a vertebral body but, through condensation and increased brittleness of the spongiosa, diminished the resistance to compression and increased the elasticity of the bone after a certain time, so that the transient elastic flattening which at first occurred with each blow recovered less and less, and the vertebra became brittle and lost its initial resistance to sudden pressure. This is analogous to the loss of temper in iron through hammering and is a physical explanation for

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8. Radmann: Zur Kenntnis der mittelbaren Wirbellbrüche, *Beitr. z. klin. Chir.* **129**:466, 1923.

9. Göcke: Traumatische Wirbelumformung in Versuch, in *Hefte zur Unfallheilkunde*, Leipzig, F. C. W. Vogel, 1931, p. 136.

diminished resistance of the vertebral body through transgression of the limit of elasticity without initial fracture of the spongiosa.

#### TRAUMA WITHOUT APPARENT FRACTURE

From physical and pathologic standpoints, where even a slight change has taken place in a vertebral body without alteration in form the affected bone is more exposed to damage by the normal daily burden. Where a change in shape has already taken place, the weakened link or bent portion throws the entire chain into static decompensation, and a more definite basis is provided for later changes. Roberg<sup>3</sup> maintained



Fig. 2.—Bilateral fracture of the femoral necks, sustained at the height of the tonic stage of a convulsion induced by metrazol shock therapy. A distinct snap was heard at the time of fracture.

that it is far more difficult for the roentgenologist than for the pathologist to separate a true fracture, associated with a single collapse and shattering of the bone trabeculae and hemorrhages, from a change in form of the vertebral body associated with a mere gradual transformation of the bone tissue. When a very evident fracture of the spine occurs, the action of the force is of such short duration that unless a fracture occurs at the time the vertebral column usually escapes without injury; however, such trauma can sometimes lead to progressive disintegration of the cancellous bone, as in Kümmell's disease, or to progressive vertebral atrophy.

## FRACTURES APPARENTLY DUE TO DIRECT VIOLENCE

Although compression fractures of the vertebral column due to direct violence are not within the scope of this communication, the following case is reported because of some interesting features.

## REPORT OF A CASE

A woman 61 years old, in the hospital for many years, suffering from schizophrenia, complained of pain in the back and tenderness in the lumbar region. Roentgen examination was indicated, which the patient refused, becoming combative, and the procedure was unsuccessful. A month later the patient still complained of pain and showed slight kyphosis. After a brief period of heavy sedation, a roentgenogram was taken, which revealed a moderate compression fracture of the eighth thoracic vertebra. The patient had not received any convulsive shock therapy, nor had she ever been seen in a state resembling a convulsion. Because the patient entertained delusions and at times had hallucination and because there had been no witnesses to the accident, the means of the injury was still obscure. The patient gave a vague account of sitting on the edge of the bed and said that some other patient, whom she was unable to identify, struck the bed forcibly, throwing her forward and thereby hurting her back. There were no visible marks anywhere on the body.

## SUMMARY

The apparently normal adult vertebral column is susceptible to gross or microscopic compressed fractures under the influence of tetanic, epileptic and metrazol-induced convulsions.

Seven cases of vertebral compression fractures sustained by muscular action during convulsions induced by metrazol shock therapy for the psychoses are reported.

A brief review of the literature and a formulation of the mechanism of vertebral compression fractures occurring in the various convulsive disorders are presented.

## EXTRA-ARTICULAR OSTEOSYNTHESIS

FOR NONUNION OF FRACTURE OF THE NECK OF THE FEMUR

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ROCHESTER, MINN.

Although the bone graft is always mentioned in any discussion concerning the treatment of ununited fractures of the neck of the femur, it has been used for only a small percentage of patients afflicted with such fractures. At the Mayo Clinic only 1 in 10 of the patients who came with ununited fractures of the neck of the femur were subjected to a bone grafting procedure. The chief reason for the infrequent use of this type of operation is that most patients with ununited fracture of the neck of the femur are seen by the surgeon when the femoral neck is practically absorbed. Local conditions at the site of fracture being thus unfavorable and the open operation (intra-articular osteosynthesis) being too extensive and complicated to be employed indiscriminately for elderly patients, the use of the bone graft has been limited to a smaller group of younger, more robust patients.

I offer no new procedure to solve the problem. This paper is presented to show that the extra-articular employment of the bone graft in a selected group of cases is practical and, accompanied as it is with little or no danger, will serve to broaden the field of usefulness of the bone graft.

Many have contributed to the literature on the bone graft. Long ago, Albee<sup>1</sup> wrote of using a carefully prepared, rounded autogenous bone graft as a peg in ununited fractures of the neck of the femur. Campbell<sup>2</sup> reported 36 cases in which treatment was by the aid of the bone graft, with 5 unknown results, 1 death, 22 successes and 8 failures. King<sup>3</sup> has advised the use of a fibular graft reenforced by a Smith-Petersen nail. Gallie and Lewis<sup>4</sup> reported 15 cases in which treatment

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From the Section on Orthopedic Surgery, the Mayo Clinic.

1. Albee, F. H.: Treatment of Ununited Fracture of the Neck of the Femur, *Surg., Gynec. & Obst.* 49:810-817 (Dec.) 1929.

2. Campbell, W. C.: Ununited Fracture of the Neck of the Femur, *Surgery* 1:499-516 (April) 1937; *Operative Orthopedics*, St. Louis, C. V. Mosby Company, 1939.

3. King, T.: The Closed Operation for Intracapsular Fracture of the Neck of the Femur: Final Results in Recent and Old Cases, *Brit. J. Surg.* 26:721-748 (April) 1939.

4. Gallie, W. E., and Lewis, F. I.: Ununited Fracture of Neck of Femur in Aged, *J. Bone & Joint Surg.* 22:76-80 (Jan.) 1940.

was by means of extra-articular osteosynthesis with use of a bone graft and a nail, with union in 6 cases and failure in 1; in the remainder the patients were either in bed or on crutches, so that the end results were not determinable at the time of his report. Dickson<sup>5</sup> advocated the use of small multiple grafts obtained from the tibia after opening the joint and provided fixation with a Smith-Petersen nail.

I recently reported<sup>6</sup> a series of cases that represented an experience of twenty-six years (from July 1913 to June 1939) in which the bone graft was used for ununited fractures of the neck of the femur. There were 77 cases in all; the end results are now known in 71. Of these, the patients in 50, or 70 per cent, obtained bony union. There were 2 deaths, a mortality of 2.5 per cent, both due to emboli. In the 2 cases in which death occurred the results were classed as failures.

Extra-articular osteosynthesis can be performed with no surgical shock, and if local conditions are favorable (that is, if the head of the femur is viable and enough of the femoral neck is present) operation of itself carries little risk even for elderly patients. Because it is necessary to have the position of the fragments and of the guide wire determined by roentgen means, the operation, often prolonged and tedious, tries the patience of the surgeon. It is the type of operation that is easy for the patient but trying for the surgeon.

Prolonged postoperative fixation in a cast, which has been considered essential, is a drawback, but I am inclined to believe that most elderly persons tolerate such fixation much better than is generally thought. Nevertheless, the stiffness in the knee and hip that follows long fixation is decidedly undesirable. Undoubtedly it would be better if fixation in a cast were not necessary and early movement of the hip and knee could be instituted.

Compere and Lee<sup>7</sup> have reported 7 cases in which treatment was by the use of several bone grafts, with two or more screw wires in addition to give fixation and thus obviate the necessity for postoperative use of a cast. Six of their patients obtained bony union. This method has the great advantage of permitting early movement, the treatment being practically ambulatory. With such a procedure the question of damaging an already devitalized femoral head by placing in it one or more bone grafts and metal nails or screws is to be considered. In

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5. Dickson, J. H.: Treatment of Ununited Fractures of the Neck of the Femur by Means of Bone Graft and Smith-Petersen Nail, *S. Clin. North America* 19:1235-1241 (Oct.) 1939.

6. Henderson, M. S.: Ununited Fracture of Neck of Femur Treated by Aid of Bone Graft, *J. Bone & Joint Surg.* 22:97-106 (Jan.) 1940.

7. Compere, E. L., and Lee, J.: The Restoration of Physiological and Anatomical Function in Old Ununited Intracapsular Fractures of the Neck of the Femur, *J. Bone & Joint Surg.* 22:261-276 (April) 1940.



1936 I used the lag screw in conjunction with the bone graft for 2 patients and obtained good results in both. They were held in a cast for six weeks before motion was permitted.

#### EXTRA-ARTICULAR OSTEOSYNTHESIS

The extra-articular method of osteosynthesis with the bone graft has been used for 14 patients at the Mayo Clinic, and my presentation concerns these patients. The average age of these 14 patients was 56 years, ten years greater than that in the group already referred to, in which treatment was by intra-articular osteosynthesis. This indicates that the surgeons were willing to undertake the risk of operation in a group of patients a decade older than when the extra-articular osteosynthetic method was used.

*Requirements Preparatory to Extra-Articular Osteosynthesis.*—Prerequisites to extra-articular osteosynthesis are: 1. The head of the

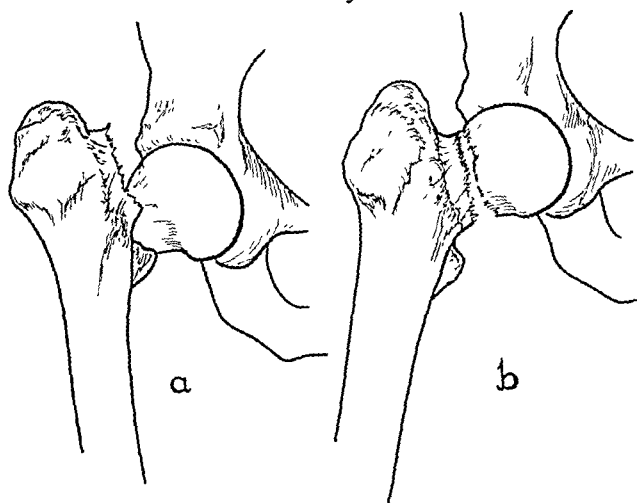


Fig. 1.—Fracture of the neck of the femur. Note (a) the upward displacement with shortening and (b) the deformity overcome by traction.

femur should have normal contour, and the roentgen findings should indicate a viable head. 2. A sufficient amount of the neck of the femur should still be present (at least a third to a fourth). 3. Complete correction of eversion must be obtained and the shortening overcome as much as possible (fig. 1). There should be roentgen evidence of proper alinement of the head and neck of the femur in anteroposterior and lateral views. Either cutaneous or skeletal traction in bed (cutaneous traction is usually sufficient) combined with maintenance of the foot and ankle in the upright position for a few days to several weeks is usually necessary (fig. 2). If such correction cannot be attained by preoperative traction, the extra-articular method should not be used. If the graft is placed with the head and neck of the femur in malalignment, the shear-

ing force during the convalescent period will be too great and the graft will break.

*Technic.*—With the aforementioned requirements fulfilled, with spinal or general anesthesia, through a lateral incision 3 or 4 inches (7.5 to 10 cm.) in length over the base of the trochanter where it meets the shaft of the femur (fig. 3 *a*), a Kirschner guide wire  $\frac{3}{32}$  inch (2.34 mm.) in diameter is inserted as nearly as possible through the center of the neck of the femur and the center of the head. The guide wires used in this clinic are all 30 cm. long. The depth to which the wire has been placed, therefore, can always be readily calculated by subtracting from 30 cm. the distance from the point at which the wire enters the bone to the exposed end of the wire. Roentgen studies are

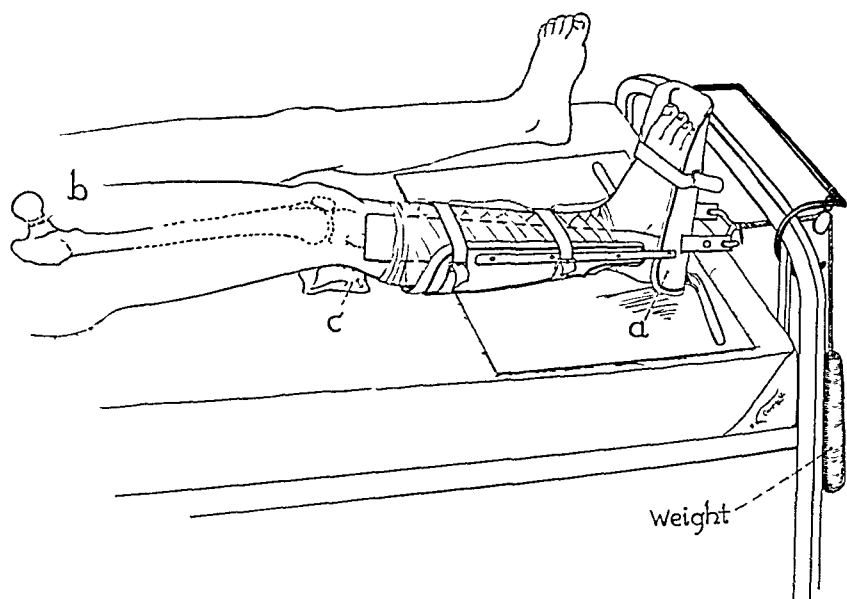


Fig. 2.—Traction maintained with a splint applied to overcome eversion. Note (*a*) the traction apparatus; (*b*) the fracture of the neck of the femur, and (*c*) the small pad to prevent hyperextension of the knee.

made anteroposteriorly and laterally to determine the position of the wire. If the position is correct, the wire is inserted deeply enough to engage the acetabular wall.

Over this guide wire, which is cut off so that it is 14 cm. in length (1 cm. short of the length of the opening of the drill), are threaded a series of cannulated drills (fig. 3 *b*), and a tunnel is made into the neck and head of the femur.

After the cannulated drills are threaded over the guide wire, the fibula on the same side is exposed in its middle third, and a segment of the proper length, usually  $3\frac{1}{2}$  to 4 inches (8.75 to 10 cm.), is removed. The fibula is approximately  $\frac{1}{2}$  inch (1.2 cm.) in diameter. This wound

should be closed immediately. The fibular graft is carefully cleansed of all muscle, and its surface is thoroughly freshened with a chisel (fig. 3 c).

The fibular graft is then threaded over the wire and is driven well into the head after a cannulated drill of the proper size had been used

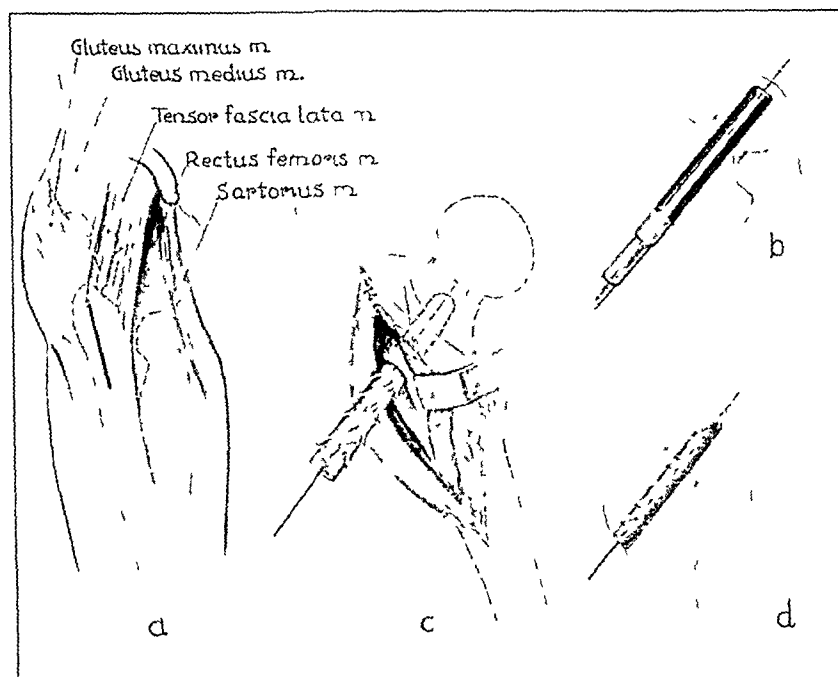


Fig. 3.—Anatomic relations of incision and bone graft. Note (a) the incision at the base of the trochanter; (b) the fibular bone graft cleansed of all muscle, thoroughly roughened and partially inserted in the tunnel prepared for it; (c) the cannulated drill inserted over a guide wire, and (d) the fibular bone graft in the proper position.

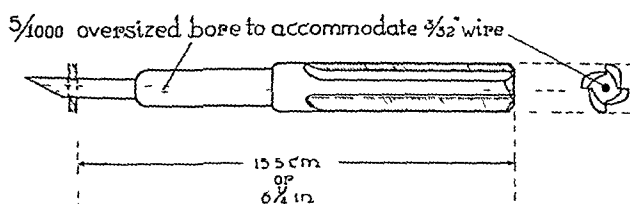


Fig. 4.—Cannulated drill.

to prepare the tunnel for its reception (fig. 3 d). A drill of the proper size should be selected in order to insure a snug fit of the bone graft in the tunnel. The fracture surfaces should then be thoroughly impacted by pounding, thus eliminating as much as possible a shearing force being applied to the graft in the course of convalescence.

The drills used here are made in the clinic's own shop of cold rolled iron, with the flutes not so deep as those of the standard types in order that an opening  $\frac{3}{32}$  inch (2.34 mm.) in diameter can be made for 16 cm. in the middle of these drills. This lumen is 0.005 inch (0.125 mm.) oversize (fig. 4). The drills are case hardened later. There are three sizes,  $\frac{3}{8}$ ,  $\frac{1}{2}$  and  $\frac{5}{8}$  inch (0.94, 1.25 and 1.56 cm.) respectively. Before the cannulated twist drill is put over the wire, the distance from the cortex of the femur to the end of the wire in the head must be determined, and the wire must be cut so that its total length will not exceed 14 cm. If it is longer than 14 cm., the drill will tend to push the wire through into the pelvis, an occurrence that has been

*Data in Fourteen Cases of Extra-Articular Osteosynthesis for Nonunion of Fracture of the Neck of the Femur*

Case	Duration of Non-union, Months	Age, Years	Sex	Date of Operation	Type of Graft	Result *	Date of Last Observation
1	7	67	F	6/20/36	Fibular	Union (E)	4/40
2	8½	58	F	9/21/36	Fibular	Nonunion (P)	3/37
3	6	57	F	9/25/36	Fibular	Union (F)	11/38
4	10	43	F	10/27/36	Fibular lag screw	Union (E)	5/40
5	13	51	M	10/28/36	Fibular lag screw	Union (E)	4/40
6	10	61	M	4/ 6/37	Fibular	Union (E)	4/40
7	5	63	F	7/31/37	Fibular	Nonunion (P)	3/40
8	7	67	F	7/15/38	Fibular	Union (E)	6/40
9	10	52	F	9/21/38	Fibular	Union (E)	2/40
10	84	49	M	1/ 5/39	Fibular	Union (E)	5/40
11	3	57	F	1/10/39	Fibular	Union (G)	3/40
12	5	62	F	4/25/39	Fibular	Union (G)	4/40
13	4	46	F	10/12/39	Fibular	Union (E)	5/40
14	8	70	F	4/23/40	Fibular	Indeterminate †	Still under observation

\* E, excellent; bony union with full function. G, good; bony union with good function. F, fair; bony union with poor function. P, poor; no union.  
† Operation too recent to report results.

reported in the literature several times. It is well to remember that the canal in the center of the drill must be carefully cleaned so that no collection of debris will narrow its lumen. If the wire does not have free play in the canal, it will bind and will be forced inward into the pelvis. Pure phenol followed by alcohol should be poured through this canal before sterilizing as an additional precaution for asepsis.

An anteroposterior roentgenogram should be taken to make sure that the bone graft is set sufficiently deep in the head of the femur. Then the guide wire is removed.

Postoperative fixation must be provided by means of a spica cast of plaster of paris that holds the leg in slight abduction with the foot in the upright position. Every bone graft goes through a period of weakness and has no real strength until at least three months after insertion.

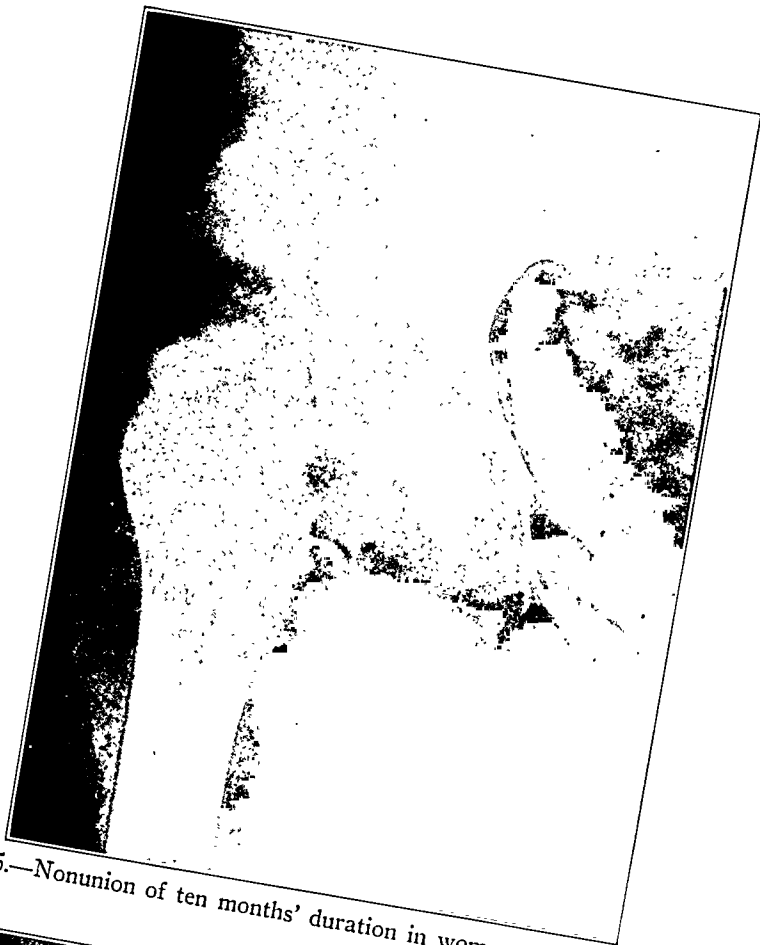


Fig. 5.—Nonunion of ten months' duration in woman aged 43 years.

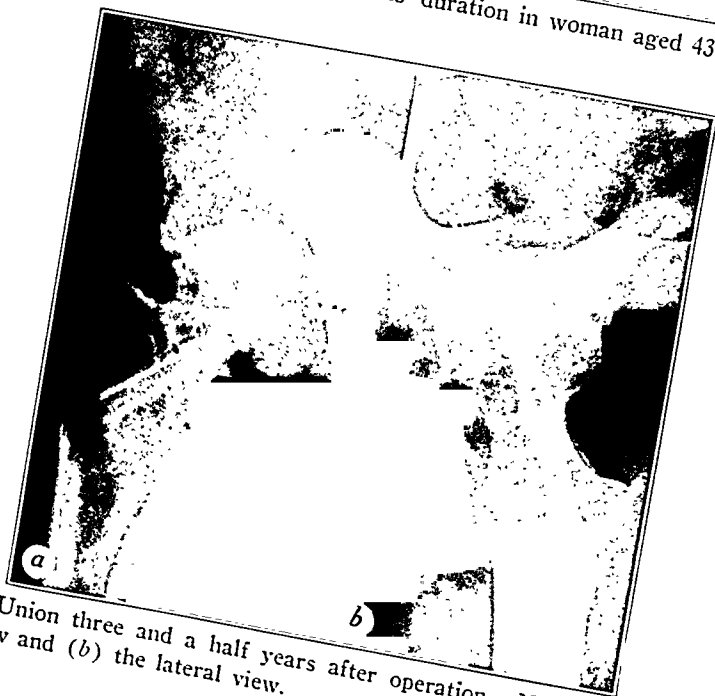


Fig. 6.—Union three and a half years after operation. Note (a) the anteroposterior view and (b) the lateral view.

During this period the graft undergoes rarefaction and partial absorption; this is promptly followed by regeneration. Weight bearing should not be permitted until six months have elapsed.

*Results.*—There were 14 patients operated on by the extra-articular osteosynthetic method (see table); their average age was 56 years. Three were in the fifth decade, 5 in the sixth, 5 in the seventh and 1 in the eighth. Eleven were women and 3 men. There were no deaths or postoperative complications of any kind. Bony union was secured in 11 cases; of these, excellent results were achieved in 8, the patients having sufficient function for all practical purposes. Two had good function but still were unable to put on their own shoes and lace them. One had only fair function, with malunion and with the leg in eversion. In the cases of 2 there was utter failure, as the grafts and the state of nonunion persisted as before. One is still in the convalescent stage (figs. 5, 6 and 7).



Fig. 7.—Nonunion of seven months' duration in a woman aged 67 years. The illustrations show (a) the appearance before operation and (b) the appearance two years after operation, with firm bony union.

*Duration of Disability.*—So many factors enter into the duration of disability that I finally gave up attempting to record the months of disability. The patients are elderly, and one therefore cannot expect too much in this respect. I am sure, however, that on the whole the duration of disability has been less and the residual stiffness of the knee and hip less in this group, in which operation was by the extra-articular method, than in the group in which the intra-articular method was used.

#### CONCLUSIONS

Extra-articular osteosynthesis carried out for 14 patients with non-union of the neck of the femur has been done, with no danger to the patients comparable to that associated with the intra-articular method.

Bony union was secured in 11 of 13 cases in which sufficient time has elapsed to determine the end result. Eight of the patients had practically normal function; the function of 2 was classified as good, that of 2 as poor and that of 1 as fair. One is not far enough along in convalescence to allow accurate judgment of what the end result will be. It is my belief that this method materially broadens the field for the use of the bone graft. Perusal of the literature definitely shows that the bone graft gives the best results in such cases, and therefore it should be used when possible.

## PERIOSTEAL FIBROSARCOMA

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Primary malignant tumors of bone constitute approximately 1 per cent of all types of malignant neoplasms.<sup>1</sup> Of this 1 per cent, an extremely small proportion is made up of periosteal fibrosarcomas. Kolodny,<sup>2</sup> in his review of the material in the Bone Registry of Sarcoma in 1928, found only a few cases. Geschickter and Copeland have stated that, among over 1,700 neoplasms involving bone, only 1.5 per cent were placed in this group. In a series of 200 primary malignant bone tumors seen at the University Hospital since 1925, comprising osteogenic sarcoma, Ewing's sarcoma, multiple myeloma and periosteal fibrosarcoma, 27 were included in the last-named group, a relatively high incidence. In every instance the diagnosis was made on the basis of a combination of clinical, operative, roentgen and histologic observations.

### GENERAL CONSIDERATIONS

The age distribution in these 27 cases was, in general, that found in most cases of sarcoma. Twenty-one patients, or 78 per cent, were under 40 years of age. Approximately one-half the patients were in the second and third decades of life. The youngest patient was 1 year of age and the oldest 76. The average age was 32 years.

There were 17 males and 10 females, or 63 per cent and 37 per cent respectively.

There was a family history of some type of malignant tumor in 4 cases; in none of these was there a history of bone tumor. In 17 cases there was no family history of malignant tumor, and in 6 cases the history was not established.

In 10 cases, or 37 per cent, there was a history of trauma. In 4 of these the trauma initiated the symptoms and might well have merely called attention to a preexisting lesion. In 2 cases the trauma antedated the symptoms by ten years; hence there was probably no relation of cause and effect. In the remaining 4 cases the trauma preceded the

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1. Geschickter, C. F., and Copeland, M. M.: *Tumors of Bone*, ed. 2, New York, American Journal of Cancer, 1936.

2. Kolodny, A.: *Bone Sarcoma*, Chicago, Surgical Publishing Company of Chicago, 1927.



symptoms by intervals varying from three to twenty-seven months. From this analysis it is evident that trauma probably does not play an important role in the development of periosteal fibrosarcoma.

#### CLINICAL MANIFESTATIONS

The average duration of symptoms was twenty months, a relatively long period as compared with the duration of other types of primary

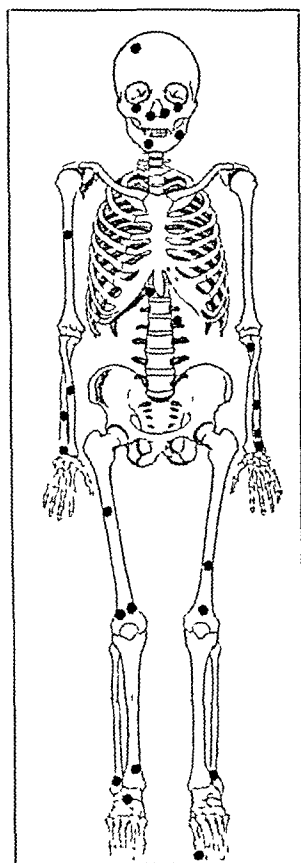


Fig. 1.—Distribution of periosteal fibrosarcoma in 27 cases.

malignant bone tumors. The shortest duration was one month; the longest was eight years. The outstanding symptoms were pain and swelling. In most instances the pain preceded the swelling, although in several cases the tumefaction was first noted. In 3 cases the presenting symptom was tumor formation without any history of pain. The pain was usually not severe, sometimes intermittent and often worse at night. The majority of patients at the time of admission to the hospital had no constitutional symptoms, such as ease of fatigue, loss of strength, anorexia or loss of weight. Four had metastases to the lungs on admis-

sion, with pain in the chest, cough, dyspnea and hemoptysis in addition to the generalized manifestations of far advanced cachexia. One patient had metastases to the regional lymph nodes on admission.

The tumor was typically deep seated, smooth and without fixation to the overlying tissues. It could be distinguished from lesions in the soft parts by its limited mobility due to its deep attachment to the periosteum. The tumor was usually firm, not hard and only moderately tender. Locally increased heat was not a marked feature. Dilatation of the superficial vessels, so often noted with osteogenic sarcoma and Ewing's sarcoma, was absent. When the tumor was in the neighborhood of a joint there was limitation of motion of that joint.

The distribution of the lesions is shown in figure 1. Without exception the lesions were single. The most common sites were the ulna and the femur, which were involved in 6 and 5 cases, respectively. The upper extremity was involved in 8 cases, or 30 per cent; the lower extremity, in 10 cases, or 37 per cent; the skull, in 7 cases, or 26 per cent; and the spine, in 2 cases, or 7 per cent. Of the lesions in the skull, 4 were in the maxilla, 2 in the mandible and 1 in the frontoparietal region. The lesions in the long bones showed a predilection, in the ratio of 5 to 3, for the ends of the bone as compared with the shaft, the distal end usually being involved.

#### ROENTGEN CHARACTERISTICS

The roentgen characteristics were largely determined by the changes in the underlying bone. These changes were of two main types, the destructive and the reactive. The more common type, the destructive, or lytic, showed a relatively large soft tissue tumor overlying an area of erosion in the contiguous cortex. The eroded area was usually smooth and involved one side of the shaft, indicating its extraosseous origin. In a few cases in which the lesions showed marked destructive changes in the bone it was impossible to rule out roentgenologically the presence of an osteolytic osteogenic sarcoma. Figure 2 illustrates the typical roentgen features of bone-destructive periosteal fibrosarcoma.

In cases of the reactive type of osseous lesion the only roentgen signs, in addition to the soft tissue swelling, were thickening and roughening of the underlying cortex, with little or no bone destruction. There was no true bone formation as seen in osteogenic sarcoma. Occasionally flakes of calcium could be seen in the substance of the tumor. Figure 3 illustrates this type of lesion.

#### PATHOLOGIC FEATURES

Periosteal fibrosarcoma arises from the fibrous layer of the periosteum, and the pathologic picture is similar to that of sarcoma arising from other connective tissue structures, such as fascial sarcoma. The



Fig. 2.—Typical roentgenogram of the bone-destructive type of periosteal fibrosarcoma.

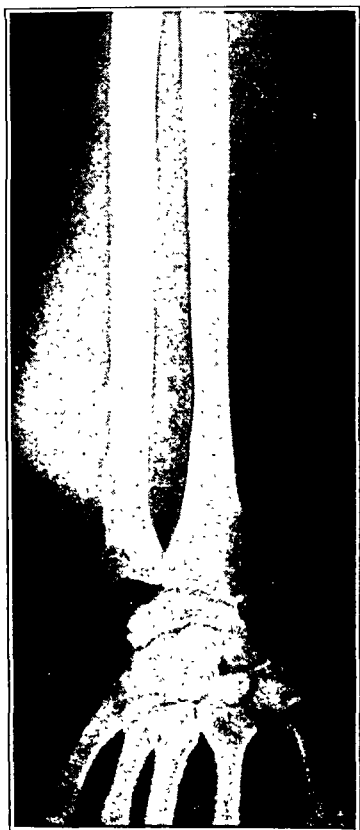


Fig. 3.—Typical roentgenogram of the bone-reactive type of periosteal fibrosarcoma.

osseous changes are secondary, although occasionally they are so extensive that they overshadow the true soft tissue nature of the lesion. Grossly, the lesions at operation were found to be firm, generally encapsulated and white and glistening on cut section, with evident whorl formation. In cases of bone-destructive lesions, as seen in roentgenograms, there was disappearance of the underlying cortex with invasion of the medullary cavity, which usually showed hemorrhagic changes. In cases of lesions showing reactive osseous changes there was frequently a sharp line of demarcation between the substance of the tumor and the underlying roughened cortex; in these cases the tumor could be shelled out with ease, although the upper and the lower limits were not well defined.

The microscopic features of periosteal fibrosarcoma were essentially the same as those of any sarcoma of fibrous tissue origin. The histologic changes were a reflection of the degree of differentiation of the cells in the process of fibrogenesis. In the most highly differentiated group the appearance closely resembled that of a benign fibroma composed of cells approaching the fibroblast type, with an abundance of collagen fibers and definite whorl formation. The somewhat less differentiated and more malignant tumors showed a decreased proportion of fibers in which the whorl formation was not marked. The least differentiated and most malignant tumors were made up almost entirely of small, closely packed, hyperchromatic spindle cells with scarcely visible cytoplasm, showed frequent mitotic figures and had practically no intercellular substance. Geschickter and Copeland have classified tumors in the various stages of dedifferentiation as fibrosarcoma, fibrospindle cell sarcoma, spindle cell sarcoma and oat cell sarcoma, the last being the most malignant type. Meyerding and Broders<sup>3</sup> have distinguished three types, the fibrous, the fibrocellular and the cellular fibrosarcoma.

In this series no attempt was made to follow either of the aforementioned classifications. The plan of distinguishing four grades, as suggested by Broders, was used, grade 1 indicating the lowest degree and grade 4 the highest degree of malignancy. The principal criteria for grading were the degree of cell differentiation, the number of mitotic figures and the relative proportions of cells and intercellular substance. Microscopic sections for grading were available in 21 cases and, as classified by Dr. Lloyd F. Catron, gave the following results: grade 1, 2 cases; grade 2, 10 cases; grade 3, 8 cases, and grade 4, 1

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3. Meyerding, H. W.; Broders, A. C., and Hargrave, R. L.: *Clinical Aspects of Fibrosarcoma of the Soft Tissues of the Extremities*, Surg., Gynec. & Obst. 62:1010-1019 (June) 1936.

case. The objection so often raised to the grading of malignant tumors, particularly sarcomas, that various grades are present in the same tumor, has much less force with regard to this type of lesion, because, as Broders has pointed out, the structure of fibrosarcoma is usually

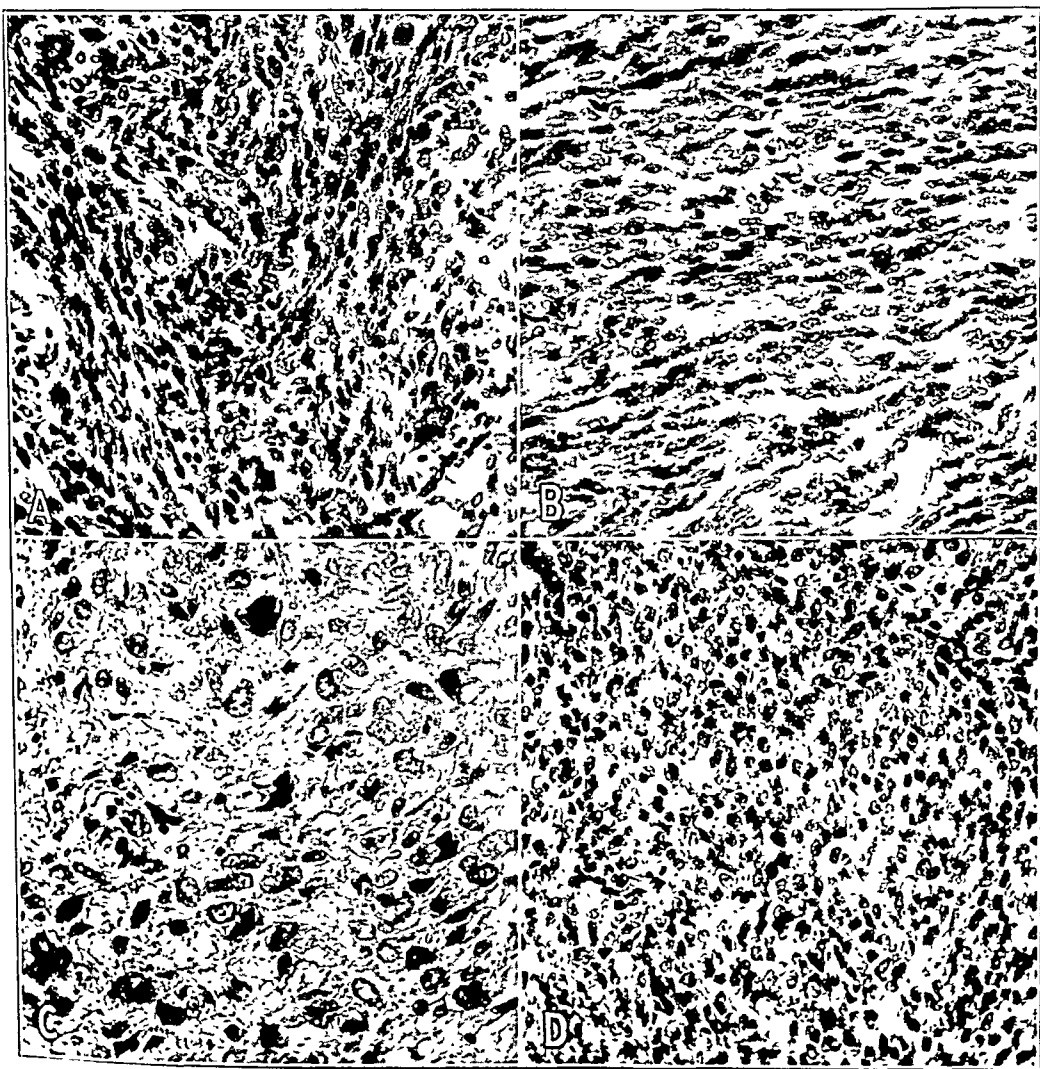


Fig. 4.—High power photomicrographs (same degree of magnification), showing the four grades of malignancy observed in cases of periosteal fibrosarcoma. A, grade 1; B, grade 2; C, grade 3; D, grade 4.

the same throughout the whole tumor. Figure 4 illustrates the microscopic characteristics of the four grades of malignancy under high power magnification.

In 3 cases in which repeated local excisions were done there was a definite progression in the grade of malignancy. Figure 5 illustrates such a change. This finding tends to support the dictum that with recurrence the tumor frequently becomes more malignant.

#### TREATMENT AND PROGNOSIS

The age of the patient, the location of the tumor, the extent of the osseous involvement, the presence or absence of metastases on admission and the degree of malignancy noted on microscopic examination were the factors which determined the type of treatment in this series. Table 1 shows the type of treatment employed and the results obtained in the 25 cases in which follow-up studies were made.

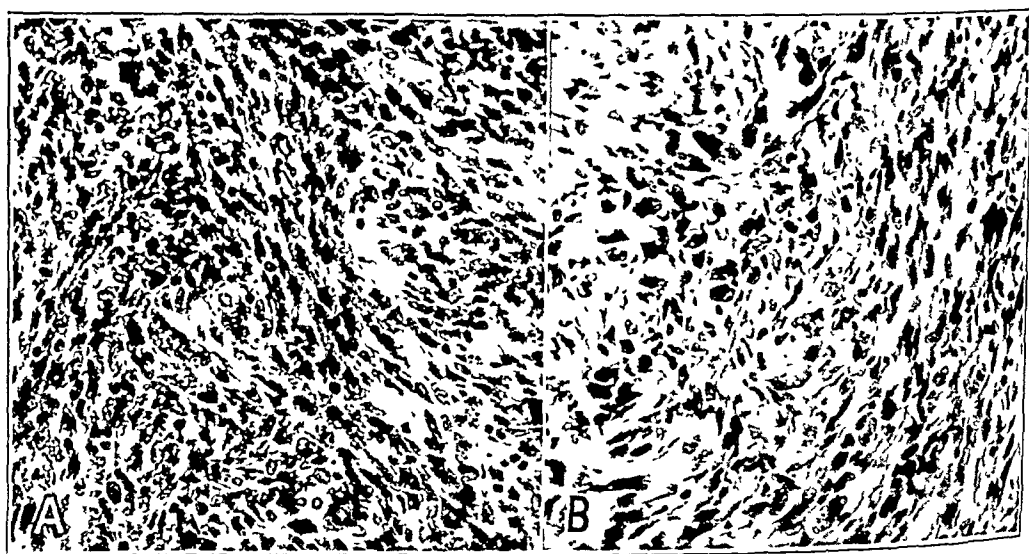


Fig. 5.—High power photomicrographs showing progression in the grade of malignancy from 1 to 3 with repeated local excision in the same patient. A, grade 1; B, grade 3.

TABLE 1.—Analysis of Twenty-Five Cases of Periosteal Fibrosarcoma Based on the Type of Treatment

Treatment	Number of Cases	Location	Mortality, per Cent	Average Survival of Living, Months	Average Survival of Dead, Months	Number of 5 Year Survivals	Percentage of 5 Year Survivals
Symptomatic.....	1	1 Upper extr.	100	..	2 days	0	0
Roentgen therapy only...	3	3 Lower extr.	67	14	12	0	0
Local excision plus roentgen therapy	10	6 Skull 2 Spine 2 Upper extr.	50	93	36	6	60
Amputation.....	11	4 Upper extr. 7 Lower extr.	45	92	26	4	36
Totals.....	25	25	52	86	28	10	40

The patient who received symptomatic treatment only was moribund on admission and died within two days.

Three patients received roentgen therapy only. In only 1 case was it the treatment of choice. The patient was a 68 year old woman with hypertension, hypertensive heart disease and a grade 3 periosteal fibrosarcoma of the femur. Fourteen months after treatment this patient reported that the tumor was giving her no trouble and that it was definitely smaller than before treatment. One patient with a tumor of the femur refused any type of treatment after biopsy except roentgen therapy. This patient died seventeen months after treatment. The third patient had far advanced pulmonary metastases on admission and died four months after treatment.

All of the patients with lesions of the spine and of the skull were treated perforce by local excision. One lesion involving the humerus and another involving the ulna were also treated by local excision; both of these lesions were of a low grade of malignancy and showed relatively little involvement of the underlying bone. The patient with the lesion of the ulna is living and well twelve and one-half years after treatment. The patient with the lesion of the humerus had a local recurrence of a higher grade of malignancy, which was treated by repeated local excision; this patient succumbed to metastases to the lungs almost seven years after the first local excision.

Local excision of lesions of the extremities was followed by amputation in 4 cases. In 1 case the amputation followed the local excision after a few days, and the amputated specimen showed no evidence of a malignant lesion. In the other 3 cases amputation was done because of local recurrence. In 7 cases a primary amputation was done at the usual sites of election.

Local excision was followed in almost every instance by roentgen therapy. The value of roentgen therapy for periosteal fibrosarcoma has never been definitely proved. It is generally supposed to be of no value. However, 3 cases deserve special mention. As has been noted, 1 of the patients who received only roentgen therapy reported fourteen months after treatment that the tumor of the thigh was definitely smaller and was causing her no trouble. The second patient had metastases to the lungs two months after a disarticulation of the hip for a lesion of the lower end of the femur. Roentgen therapy to the chest resulted in complete disappearance of the pulmonary lesions, and a check-up examination fourteen months later showed no evidence of their recurrence. The third patient received roentgen therapy to a large tumor arising from the spine, which showed a 75 per cent reduction in size before local excision was carried out.

Follow-up studies were made in 25 cases, or 93 per cent, of this series. At the time of writing, 12 patients, or 48 per cent, were living,

and 13, or 52 per cent, had died. Among the living, the average duration of the disease from the onset until the time of writing was one hundred and two months, and from the time of treatment until the time of writing, eighty-six months. Among those who subsequently died, the average duration of the disease from the onset until death was forty-seven months, and from the time of treatment until death, twenty-five months. Ten patients survived more than five years after treatment, an incidence of 40 per cent. The fact that 3 of these 10 patients died of their malignant lesions more than five years after the institution of treatment is another demonstration of the absurdity of the designation "five year cures."

The patients who died succumbed for the most part to metastases, which were almost invariably to the lungs. Five patients had metastases on admission, 4 to the lungs and 1 to the regional lymph nodes and later to the lungs. Of the remaining 8 patients, 4 had metastases

TABLE 2.—*Analysis of Twenty-Five Cases of Periosteal Fibrosarcoma Based on the Location of the Lesions*

Location	Number of Cases	Mortality, per Cent	Number of 5 Year Survivals	Percentage of 5 Year Survivals
Spine.....	2	100	0	0
Skull.....	6	33	5	83
Upper extremity.....	7	71	3	43
Lower extremity.....	10	40 (60%)	3	30

to the lungs subsequent to treatment, while in the cases of the other 4 the precise mode of death was not established.

To determine the prognosis of periosteal fibrosarcoma an attempt was made to evaluate the following factors: the duration of symptoms prior to admission and treatment, the location of the lesion, the type of treatment and the grade of malignancy. Among the patients who were living at the time of writing, 80 per cent had had symptoms for six months or less from the onset until admission to the hospital. Among those who died, 75 per cent had had symptoms for a year or more prior to admission. This supports the rather obvious contention that treatment, to be effective, must be started early in the course of the disease.

An analysis of the end results based on the location of the tumor furnished the results shown in table 2. The lesions affecting the spine were relatively inaccessible, and no more than a partial excision could be done. The lesions affecting the skull were more accessible, and in spite of the fact that local excision was carried out in each case, accompanied with roentgen therapy, the results of treatment were excellent. On the other hand, the lesions of the extremities, which were treated in the majority of cases by amputation, were associated with a much higher mortality and a much smaller percentage of five-year survivals.



The results with lesions of the lower extremity were really less favorable than is indicated, because 2 of the patients who were living had metastases to the lungs. It is evident that, with the exception of the lesions in the spine, the location of the tumor was probably not the determining factor in the outcome of the disease.

It will be noted from table 1 that the mortality among those patients who had a local excision plus roentgen therapy was approximately the same as among those who underwent amputation, while the percentage of five year survivals was much higher among those who were treated by the less radical procedure. It seems justifiable to conclude that the particular type of treatment employed was not the most important factor in determining the outcome of the disease, since amputation should result in a more favorable prognosis for life.

TABLE 3.—*Analysis of Twenty-One Cases of Periosteal Fibrosarcoma Based on the Grade of Malignancy*

Grade of Malignancy	Number of Cases	Mortality, per Cent	Average Survival of Living, Months		Average Survival of Dead, Months		Metastasis		Number of 5 Year Survivals	Percentage of 5 Year Survivals
			After Onset	After Treatment	After Onset	After Treatment	On Admission	After Treatment		
1	2	50	106	100	67+	67	0	0	2	100
2	10	20	120	85	65	48	0	1	7	70
3	8	63	22	14	27	11	3	3	0	0
4	1	100	..	..	6	3	0	1	0	0

Table 3 offers a striking indication of the influence of the grade of malignancy of the tumor on the prognosis. The mortality was much greater for the higher grades of malignancy. The 63 per cent mortality for grade 3 will undoubtedly increase to 88 per cent, because 2 of the 3 living patients had pulmonary metastases. The average survival periods for the living and the dead were in inverse proportion to the grade of malignancy. Of the patients who had known metastases, all but 1 had lesions of grades 3 and 4. All of the patients who survived for as long as five years had lesions of grades 1 and 2. It should be noted that the grades of malignancy were determined without reference to any but the microscopic features of these tumors.

The implications of the grade of malignancy for treatment are that more conservative measures, such as local excision, with or without roentgen therapy, may be attempted with grades 1 and 2; tumors of the higher grades of malignancy should be treated by more radical means, namely, amputation when possible and the widest possible local excision in locations in which amputation is impossible. The determination of the grade of malignancy is made from fixed microscopic sections; hence a few days must elapse between the taking of a biopsy specimen and the final treatment. In those cases in which the decision

between local excision and amputation rests on the grade of malignancy it is considered permissible to wait a few days, as the danger of a short delay between the removal of a specimen for biopsy and the curative operation has never been established.

#### SUMMARY AND CONCLUSIONS

Periosteal fibrosarcoma is an extremely rare lesion, in this series constituting 1 of every 8 primary malignant tumors of bone. Approximately 75 per cent of the lesions occurred in patients under 40 years of age, the greatest incidence being in young adult life. The sex incidence was almost 2 to 1 in favor of males. The family history was not significant, nor did trauma play an important role. The average duration of symptoms before the diagnosis was established was twenty months. The outstanding symptoms were pain and swelling. The chief physical finding was a firm, deep-seated, smooth tumor without fixation to the overlying tissues but with deep attachment to the periosteum. The lesions were single and occurred most frequently in the extremities, although approximately 25 per cent occurred in the skull. The roentgen characteristics were those of a large soft tissue tumor with either lytic or reactive changes in the underlying bone, the destructive changes being more common. At operation the lesion was found to be firm, generally encapsulated and white and glistening on cut section, with occasional hemorrhagic changes. There was usually destruction of the underlying bone. The microscopic features were essentially the same as those of any sarcoma of fibrous tissue origin.

The treatment consisted, usually of either local excision or amputation. Roentgen therapy was the usual adjunct to local excision and for inoperable lesions was used as a palliative measure. The choice of treatment depended on the age of the patient, the location of the tumor, the extent of the osseous involvement, the presence or absence of distant metastases and the degree of malignancy noted on microscopic examination. The mortality was approximately 50 per cent, and the incidence of five year survivals was 40 per cent. Death was usually due to pulmonary metastases. The grade of malignancy, as noted on microscopic examination, was the most important feature in determining the prognosis. All of the patients who survived for five years or more had lesions of a low degree of malignancy.

## A CASE OF INGUINAL ENDOMETRIOMA

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Since Cullen first described inguinal endometrioma, there have been several cases reported in the literature. This lesion is of general surgical interest, for the preoperative diagnosis has usually been incarcerated inguinal hernia, whether or not a hernia sac was actually present. The aspect of the subject which has gained most attention, however, is the search for an explanation of the pathogenesis.

Sampson mentioned five possible theories which could account for the presence of endometrium in the region of the external inguinal ring: 1. Muellerian tissue might be placed beside the round ligament as a result of faulty embryonic development. 2. Mesothelium in the region of the round ligament might undergo metaplasia. 3. Pelvic endometriosis could reach the groin by direct growth extension. 4. Endometrial metastasis could take place by way of the blood or lymph vessels. 5. If a hernia sac were present, an endometrial implant could reach the groin by way of the peritoneal cavity.

Sampson observed 2 cases of inguinal endometrioma in which there were associated hernias. In 1 instance endometrial implants were found in the wall of an inguinal hernia sac. In the other case a femoral hernia was present on the same side, but the endometrioma appeared to be free of the hernia sac. Christopher reported 1 case and Hilgenfeldt 2 in which endometrial implants were found in inguinal hernia sacs. Polster observed 2 cases of endometrioma attached to the round ligament outside the external inguinal ring in which there was inguinal hernia of the same side, without, however, evidence of serosal implantation. Knoflach reported a similar case.

Sampson presented 1 case of endometrioma of the groin in which endometrial tissue appeared to have reached the inguinal region by direct growth extension through the inguinal canal. The patient had extensive pelvic endometriosis, with implants against the internal inguinal ring. Continuity was apparent between the pelvic endometriosis and the mass in the groin. Kaulich and Gomori reported a case in which

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they observed histologic evidence of endometrial growth along the round ligament.

Cases of inguinal endometrioma have been reported by Cullen, Beck, Blumer, Henry, Meigs and Schmitz in which there was neither a hernia sac nor evidence of endometrial growth extension through the inguinal canal. To explain the presence of endometrial tissue in the groin in



Inguinal endometrioma.

these patients one can refer to the other three possibilities mentioned by Sampson: the congenital rest theory, metaplasia and metastasis. Convincing evidence in favor of any of these theories is lacking.

#### REPORT OF A CASE

Our patient was a married woman 28 years of age. She was first seen in February 1938. Aside from an attack of colitis that persisted in 1936 and 1937 she had always been well. She had had no pregnancies and no menstrual irregu-

larities or complaints. She complained of pain and of swelling of one month's duration in the right groin. The pain was dull and was more severe at the onset of the menses. She felt that the swelling was about the size of an egg. Coughing, laughing or touching the mass produced pain. Examination showed her to be well developed and well nourished, weighing 130 pounds (59 Kg.). The only abnormal finding was a right inguinal hernia. This was operated on in February 1938, and a sac the size of a lemon was found. Digital examination of the pelvis revealed no pathologic condition. Recovery was uneventful.

Two years later, in January 1940, the patient returned, stating that she had enjoyed good health since the hernia repair but that she had always had some pain in the right groin, that a small lump was palpable and that at her menstrual time there was more pain and the lump increased in size. Examination revealed a mass about the size of a peanut kernel just to the right of the pubes. It was slightly tender when pressed against the pubic ramus. The patient stated that it was definitely larger, and extremely painful, during menstruation.

With the patient under a general anesthesia, an incision was made over the right pubic spine, and the dissection was carried down to a small mass the size of an olive which was in the region of the external ring. The tissues as encountered were adherent in scar as a result of the previous hernia repair. To facilitate dissection the incision was extended obliquely upward, and the course of the round ligament was followed. A part of the round ligament and the tissue mass were then excised. Twice during the procedure small quantities of chocolate-colored fluid were encountered, suggesting the possibility that this tissue was an endometrial implant. The deeper structures were then closed with catgut and the skin with silk.

*Pathologic Report.*—The specimen consisted of a piece of fibroblastic tissue with some fat attached, which measured 3 by 2 cm. The tissue was firm and fibrous in places, and there no distinct tumor masses were seen. On section through the tissue, the cut surface showed some brown hemorrhagic discoloration. Sections were taken for microscopic study.

Under the microscope the section was seen to consist for the most part of fibrous and fatty tissue. In places there were elongated and dilated acini lined by columnar epithelium and surrounded in part by tissue resembling endometrial stroma.

The diagnosis was endometrioma.

The patient made a good recovery from the operation and has had no complaints since.

#### COMMENT

This case appears to be similar to those reported by Sampson, Polster and Knoflach, in which endometrioma of the round ligament was associated with the presence of a hernia sac, without, however, evidence of serosal implantation. The possibility exists, of course, that an endometrioma within a hernia sac might afix itself to the round ligament and then undergo partial atrophy, thus leaving the hernia sac free. On the other hand, several cases of endometrioma of the round ligament have been reported in which there was no associated hernia, and the presence of these two lesions in the same patient may have been mere coincidence.

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## TIMING OPERATIVE INTERVENTION FOR ACUTE INTESTINAL OBSTRUCTION

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The rather voluminous literature on intestinal obstruction has in recent years undergone a great change. Only a few years ago, Fred T. Murphy said in Ochsner's "Surgical Diagnosis and Treatment:"<sup>1</sup> "For a mechanical obstruction of the bowel, there is no other logical treatment than operation for the relief of the obstruction." The recent literature, however, has shown what a great mistake this was and attests the splendid results obtained by the use of peroral suction of the upper portion of the intestinal tract. The teachings of Wangensteen,<sup>2</sup> Johnston<sup>3</sup> and many others are now so well established and have been confirmed in so many clinics that one must accept them; they require no further proof. Nevertheless, in almost every article dealing with the "conservative" treatment of intestinal obstructions one finds the statement that this is not to be used as a complete substitute for the operative treatment. Wangensteen<sup>4</sup> wrote: "Operation still is, and probably will continue to be the chief mainstay of therapy in most forms of bowel obstruction." This thought is echoed by most of the writers who extol the values of conservative methods. It is, however, difficult to determine in which cases operation should be done immediately and in which cases conservative methods should be attempted and when they should be abandoned for operative intervention. In an attempt to clarify this issue, the following study was undertaken.

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We first tried to classify the types of intestinal obstruction from the therapeutic standpoint and then attempted to find certain clinical signs which would permit such a clinical grouping (table 1). These signs were gleaned from a review of a series of case records in the files of the Cook County Hospital. We have not discovered any new signs, nor have we in this review contributed any new methods; rather, we are attempting to present a working plan for integrating the individual case of intestinal obstruction into the therapeutic plan and to present a few examples which demonstrate the workability of this procedure.

As will be observed from table 1, we classify intestinal obstructions into: (1) those urgently demanding operative intervention; (2) those to be treated conservatively for an arbitrary period, and (3) those to be managed entirely by conservative methods or operated on at a time of election. That is, we determine whether by the symptom complex the condition fits into the first group; if it does not, it falls automatically into the group for which delayed treatment is permissible. At any time during

TABLE 1.—*Classification of Therapy for Acute Obstruction of the Bowel\**

1. Immediate Operation	2. Delayed Operation	3. Conservative Treatment
Complete colonic obstruction	Internal hernias	Bands and adhesions
Strangulation obstruction	Obturation by foreign body	
Intussusception	Internal pseudohernia	
Intestinal atresias		

\* This classification is by no means hard and fast as strangulation may develop in the patient who has an internal hernia or even an adhesion band, thus classifying the condition in group 1.

the period of expectant therapy the patient may present additional signs which automatically advance his condition into the urgent group. At the end of the arbitrary time, which we have set at forty-eight hours, the clinical status is reviewed to determine whether the condition now belongs in the "delayed" group or passes on into the "conservative therapy" group. We cannot, however, emphasize too strongly that at any time in the course of conservative therapy there may be urgent indications for intervention. This necessitates constant observation, and the surgeon cannot relax his vigilance in the feeling of false security that is often engendered by the use of the suction catheter and intravenous fluids.

In this discussion we shall make no mention of external hernias, although they are a major etiologic factor in intestinal obstruction. Their diagnosis should not be fraught with difficulty in most instances, and their care forms a separate chapter of surgical therapeutics. Reference will later be made, however, to two important complications of the manipulative reduction of external hernia, namely, reduction of gangrenous bowel and reduction en masse.



## CONDITIONS URGENTLY REQUIRING OPERATIVE INTERVENTION

1. *Complete Obstruction of the Colon.*—Complete colonic obstructions must be, as Wangenstein<sup>1</sup> has pointed out, considered as closed loop obstructions. This is true because of the invariable competence of the ileocecal valve in the presence of obstruction of the colon. Therefore, if the obstruction is truly complete, tremendous distention will usually take place. This cannot be relieved by vomiting, nor will the Levine catheter and suction be of any avail. We have not observed any reports of a Miller-Abbott tube being passed through the ileocecal valve in the face of a colonic obstruction, although this is not inconceivable. Most colonic obstructions are not truly complete. In the majority of cases (86.7 per cent in Burgess' <sup>2</sup> series) the obstructing lesion is an annular carcinoma of the left side of the colon, the lumen of which has become obturated by fecal material, often of vegetable origin. This obturation often can be washed free by enemas, which transforms the complete obstruction into a chronic or partial obstruction, and can then be treated accordingly.

The diagnosis of colonic obstruction is based on the following clinical picture. The patient is usually of middle age or advanced years and has often been a sufferer from constipation and abdominal discomfort for some time. Often there is a history of successive attacks of partial obstruction, which have been relieved by catharsis or by enemas. In many instances a history of blood and mucus in the stool or of diarrhea is obtainable. Vomiting is usually very slight, considering the degree of distention. The patient frequently does not look as ill as the findings would suggest. On physical examination the abdomen is found to be distended and smooth. The distention goes well out into the flanks, while the umbilicus may not be very much raised above the xiphopubic level. The abdomen is soft, and tenderness, if present, is in the cecal area. Rushes of peristalsis will be heard in practically all cases, but, as Vaughan and Thorek<sup>3</sup> have pointed out, the interval between the rushes may be considerable, necessitating auscultation for five minutes or more. Digital rectal examination may reveal the neoplasm in the rectum, although carcinoma of the rectal ampulla does not as a rule produce acute obstruction. Tympany will extend into the lumbar region, and scratch sounds may also be heard well into the lumbar area. Dulness of the liver is usually reduced and may be absent.

The diagnosis can usually be confirmed by the use of a 2 quart (1.8 liter) tap water enema. The normal colon will accommodate itself to this amount, but a patient with an obstructive lesion of the left side of

5. Burgess, A. H.: Discussion of the Treatment of Obstructions of the Colon, Brit. M. J. **2**:547 (Sept. 29) 1923.

6. Vaughan, R., and Thorek, P.: Abdominal Auscultation, Am. J. Surg. **45**: 230-234 (Aug.) 1939.

the colon will usually permit only a fraction of this amount of water to be given, on account of pain incident to distention by the enema. Some surgeons are reluctant to make use of the tap water enema, fearing a perforation. This is not to be feared with the obstructive lesions as a rule, because the point of perforation (and thus the point of weakness) is either the cecum (Wangensteen<sup>1</sup>) or the point of the stercoral ulceration just above the obstructing lesion. The enema, however, in the presence of complete colonic obstruction does not pass the carcinoma and is, therefore, innocuous. The diagnosis is furthered by the flat plate of the abdomen. It is true that in rare cases a small amount of gas will be observed in the terminal portion of the ileum, but usually the gas pattern is entirely colonic.

This can be differentiated in the manner suggested in table 2. Wangenstein depreciated the information given by the barium sulfate enema. We have, however, found it valuable in several cases, especially

TABLE 2.—*Roentgen Signs of Obstruction of the Small and of the Large Bowel*

Small Intestine	Large Intestine
Paralleling of loops	Inverted horseshoe configuration
Valvulae conniventes *	Haustral markings *
Stepladder fluid levels	Large fluid levels

\* The valvulae conniventes are seen as small indentations in the gas pattern. If one carefully observes the outside of the bowel wall, which will appear as a gray shadow, one can see that it describes a straight line (fig. 2). This is caused by the valvulae, which are folds of mucous membrane. In contrast, the haustral markings will be observed as much larger indentations which are from the outside of the colon (fig. 3). The haustra are caused by the shortening of the colon by the inflexible length of the taenia coli.

those in which it is difficult to establish the diagnosis of small or large intestine in the flat plate of the abdomen.

It will be noted that the administration of the tap water enema is both a diagnostic and a therapeutic procedure, for it will often transform an apparently complete colonic obstruction into a chronic one. We should also like to emphasize that tap water, not soapsuds, is used. The latter type of clysis is irritating, and a spastic type of obstruction will react badly. Also, the irritating substance makes it difficult to use the entire 2 quarts even in a normal colon, which will easily accept a similar amount of warm tap water. The only contraindication to the use of such enemas is the suspected presence of a perforation. As we have pointed out in a previous report,<sup>7</sup> this is to be suspected in the presence of signs of peritonitis.

2. *Strangulation Obstruction.*—There is but little argument that strangulated loop obstruction must be subjected to emergency operative intervention. The only time to be expended in preparation is that

7. Koucky, J., and Beck, W. C.: Acute Nonmalignant Perforations of the Colon, *Surgery* 7:674, 1940.

required to replenish the loss of blood. The diagnosis of a strangulated loop is made on the diagnosis of an intestinal obstruction (intestinal colic with vomiting and/or distention and/or obstipation) combined with the signs of peritonitis. It is probable that there are only very rare cases in which the arterial blood is completely shut off in the presence of strangulation. In nearly all instances the venous circulation is disturbed and there is a tremendous passive congestion, which soon gives way to hemorrhage, first into the tissues of the intestine and then into the lumen of the intestine and into the free peritoneal cavity. This initiates aseptic peritonitis. The cardinal signs of peritonitis are tenderness, rebound tenderness and paralysis of the intestines, that is, a silent abdomen. We have observed tenderness and rebound tenderness in a few cases of simple obstruction even before the peritoneum was grossly contaminated. In a series of 35 cases of strangulated loop intestinal

TABLE 3.—*Symptoms and Signs of Strangulated Loop Obstruction (35 Cases)*

History of cramping pain. ....	35
History of borborygmi audible to patient .....	10 *
Vomiting.....	33
Obstipation ... ..	32
Distention.....	27
Tenderness... ..	32 †
Rebound tenderness . . . . .	30 †
Fever (rectal temperature above 99 F) . . . . .	27
Leukocytosis... ..	24
Increased sediment rate . . . . .	6 (of 10 studied)
Silent abdomen . . . . .	35

\* Probably an incomplete statistic, as this is not often asked for or volunteered.

† Response in other cases definitely noted as negative.

obstruction (table 3) there were 5 cases in which rebound tenderness was entirely absent and 3 cases in which no tenderness was exhibited. In all of the 35 cases, however, the abdomen was silent to five minute auscultation. The systemic reaction varied, 27 of the 35 patients having a febrile reaction and 24 having polymorphonuclear leukocytosis. The sedimentation rate of the red blood cells we have found to be a completely unreliable guide.

As these patients in most instances entered the hospital after the strangulation was already in existence, they presented the signs of peritonitis with paralytic ileus. We have found this a most difficult condition to differentiate (case 1). The history may be significant. The patient may state that at the onset of the disease there were intermittent cramping pains associated with rumbling sounds in the abdomen. These sounds may have been audible to the patient or to a relative at the onset of the disease. A patient with acute appendicitis will often have cramping pains at the onset, but these are rarely associated with borborygmic sounds. The most valuable aid to the diagnosis will be the flat plate of the abdomen, for in cases of strangulation of the small

bowel, only the small intestine will appear distended (fig. 1), while in cases of bacterial peritonitis both the small and the large bowel (fig. 2) will be distended (table 2). In the case of a volvulus, only a huge distended loop will be seen, which resembles neither small nor large intestine.

Under the heading of strangulated loop obstruction belong two other lesions which from their physical and roentgen signs are indistinguish-



Fig. 1.—Roentgen film showing an obstruction of the small bowel. Note the paralleling of the loops. Note the absence of gas in the large bowel in the flank. The film was taken with the patient in the horizontal position.

able from volvulus. They are venous mesenteric thrombosis and reduced strangulated hernia. The former may be slow in onset or may follow a fulminating course. The lesion occurs primarily in patients with diseased hearts and is well nigh hopeless. The diagnosis of a reduced strangulated hernia, when it has been reduced by the surgeon, is self evident. Cases of spontaneous reduction in the presence of strangulation are recorded but are too rare to be considered. The patients present the classic signs of mechanical obstruction plus those of peritonitis.

3. *Irreducible Intussusception.*—This condition is a variety of strangulation obstruction, but the strangulated loop in this instance is encased in normal intestine. Thus the hemorrhage does not reach the free peritoneal cavity but is passed into the fecal current and is observed in the stool. It is not in the province of this paper to discuss the diagnosis of intussusception, as it has been adequately reviewed in nearly all surgical textbooks.

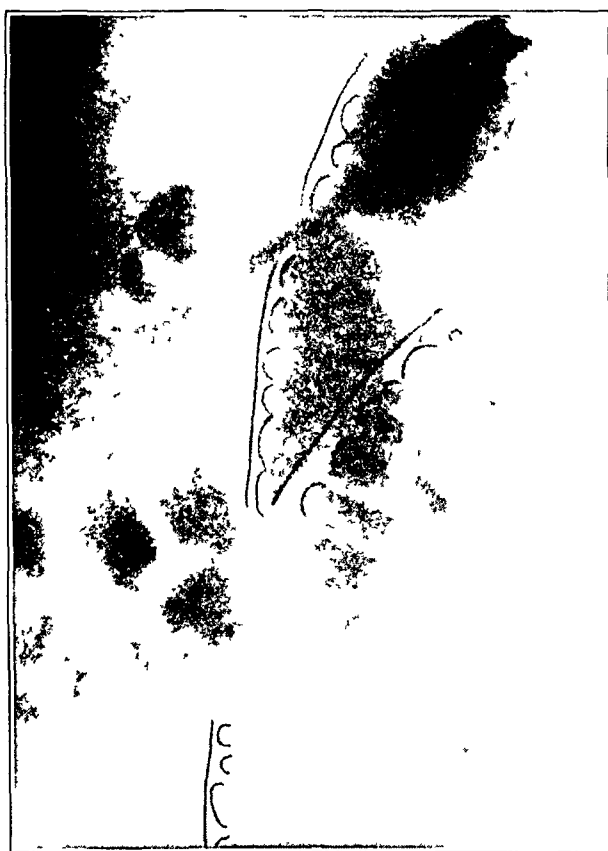


Fig. 2.—Detail film showing the pattern of an obstruction of the small bowel. Note the valvulae conniventes and the outside of the bowel, which does not assume the configuration of the valvulae but rather assumes a straight line. This has been demonstrated by a line drawn on the picture.

4. *Conditions Eventually Surgical.*—Wangensteen has pointed out that nothing is gained by delaying operation for atresias of the intestinal tract, including imperforate anus, and these should therefore be subjected to operative intervention as early as the diagnosis has become established.

## CONDITIONS AMENABLE TO DELAYED OPERATIVE INTERVENTION

Into this group fall those conditions associated with symptoms and signs which do not place them in the urgent group. As has already been stressed, the patients may become imperatively in need of operation, and the signs of peritonitis, namely, tenderness, rebound tenderness and disappearance of the intestinal sounds, must be constantly looked for. During the period of conservative therapy, the treatment is



Fig. 3.—Detail film showing the pattern of a haustrum in a case of obstruction of the large bowel. Note that the outside of the intestinal wall follows the haustral contour and is indented. This has been demonstrated by lines drawn on the picture.

essentially as has been outlined by the many authors in this field.<sup>8</sup> We add to the usual therapy the parenteral administration of vitamin K. At four hour intervals the patient's tube is clamped off for one-half hour; 2 ounces (60 cc.) of liquid petrolatum is injected through the tube (as suggested by Vaughan), and the patient is given a tap water enema.

8. Wangenstein and others.<sup>2</sup> Johnston and others.<sup>3</sup>

These enemas are discontinued if they cause the patient much discomfort. The amount of distention as related to the contour of the abdomen and to the xiphopubic line is noted. Another flat plate of the abdomen is made in forty-eight hours, and at this time the clinical status of the patient is reviewed. The signs of systemic reaction, the pulse rate, the temperature and the leukocyte count are checked. If the patient is beginning to show signs of toxicity, operation is believed to be indicated. If the dis-

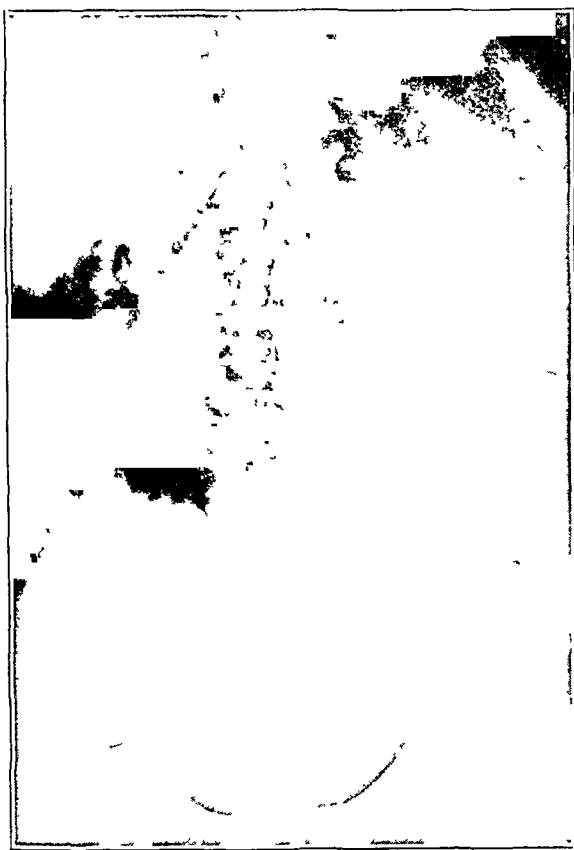


Fig. 4—Roentgen film showing a volvulus of the sigmoid flexure. Note the huge gas pattern of double contour having its apex in the left upper quadrant but its root in the left lower quadrant. No other lesion presents a similar picture.

tention has not improved, as observed by the abdominal contour or by the amount of gas seen in the flat plate of the abdomen, operative intervention is believed to be indicated. Also, if the intestinal tract, as evidenced by the recovery of oil administered through the tube and obtained by the enema, is not yet open, we believe that the patient should be subjected to operation.

In this group we have found that the cause of the obstruction is usually obturation by a gallstone or a foreign body, an internal hernia or

a loop of intestine which has slipped under an adhesive band, forming a sort of pseudohernia (case 3). Also in this group will fall the condition seen in patients on whom reduction en masse has been performed after an attempt at manual reduction of external hernias.

#### CONDITIONS AMENABLE TO CONSERVATIVE THERAPY

Into this group will fall all of the conditions which show some response to the conservative method during the first forty-eight hours. It will be found that this is the largest group and that most patients with intestinal obstruction will have a recovery of oil in the enemas within this time. Into this group will fall nearly all of the postoperative intestinal obstructions and those due to kinks and bands. In a small percentage of the cases, however, the obstruction will recur as soon as the suction is discontinued, even if this is maintained for a long period. Operation is best performed at a time of election, that is, when the fluid, electrolyte, protein and vitamin balance has been adequately controlled.

#### REPORTS OF ILLUSTRATIVE CASES

CASE 1.—A Negro aged 32 years entered the Cook County Hospital in February 1940. He had been under treatment previously for several months for polyposis of the colon. On the afternoon of admission he underwent fulguration of a polyp in the upper part of the rectum. About six hours after this treatment, there suddenly developed acute abdominal pain.

The physical findings at this time were those associated with perforation of the colon. Recovery was secured by exteriorizing the perforated segment. About four weeks after the operation the patient again suddenly had severe pains in the abdomen. This abdominal pain was mostly in the epigastrium and was cramping. With each of these abdominal cramps peristalsis was audible all over the room. The abdomen was flat, but within an hour it seemed slightly distended. The patient did not pass any gas through his colostomy opening, but an enema administered through this opening went in with ease, and the patient retained approximately 1,000 cc. Auscultation of the abdomen revealed definite rushes of high-pitched tinkling sounds. A flat plate of the abdomen revealed distention of the small intestine in the upper right portion of the abdomen. Approximately four hours later, in spite of Wangenstein suction and intravenous fluids, the patient appeared worse. Auscultation of the abdomen at this time revealed a complete absence of intestinal sounds. At this time the abdomen was also becoming tender and showed evidence of rebound tenderness. The patient was, therefore, prepared for emergency operative intervention, with a diagnosis of a strangulated loop of intestine, which probably had slipped alongside the colostomy.

At the operation the peritoneal cavity was filled with blood-stained fluid. A loop of about 5 feet (160 cm.) of strangulated intestine (not gangrenous) was found and eviscerated. It was found that this loop of intestine had become twisted and at the apex of the volvulus was Meckel's diverticulum, which contained a penetrating ulcer at its apex. This penetrating ulcer had become adherent to the anterior abdominal wall and thus formed an anchor point for the volvulus. The loop was untwisted, the diverticulum resected and the abdomen closed. The patient made an uneventful recovery.



*Comment.*—This case was interesting because we were able to observe the development of the signs of peritonitis from their inception. At first we had only the evidence of an intestinal obstruction without the manifestation of peritonitis. After four hours, however, the abdomen exhibited tenderness and rebound tenderness and became completely silent. Had we seen this patient later, after the peritonitic signs had developed, it would have been possible to differentiate the strangulated



Fig. 5 (case 1).—Roentgen film of a volvulus of the small bowel. Note the two opposed loops of gas-distended intestine. In this case there was pseudoknotting in which two loops were strangulated. The gas in the upper part of the film is judged to be in the stomach.

loop from peritonic ileus only by the roentgenogram, which was typical (see report of case 5).

CASE 2.—A 65 year old white man entered the Cook County Hospital in January 1940. He stated that he had been perfectly well until six months before admission, at which time he noticed that he was becoming increasingly more constipated. He found that he had to take liquid petrolatum and then magnesium hydroxide almost daily in order to keep his bowels open. Five days before

admission he noticed cramping pains in the abdomen, which he attributed to gas. These cramping pains were often associated with loud gurgles which he could definitely hear. On the first day of this period he passed small amounts of gas, but after this he had been unable to have any bowel movement or to pass any gas. He also noted that his abdomen became more and more distended. He lost his appetite and on one occasion vomited, although only a very small amount. There had been no previous surgical intervention and no previous illnesses that he remembered.

On physical examination he was found to be rather emaciated. He looked older than the age given. Examination of the chest revealed a somewhat enlarged heart and muffled heart tones. Examination of the abdomen showed it to be grossly distended, the distention going well out into the flanks. He had a small direct inguinal hernia, which was easily reducible. No femoral hernias were evident. Percussion of the abdomen revealed it to be tympanitic throughout, with a marked reduction of hepatic dullness. Palpation did not reveal any tumor masses or areas of tenderness or rigidity. On auscultation there were high-pitched borborygmic sounds, which came in rushes and were separated by long silent periods. Rectal examination gave entirely negative results except for a slightly enlarged prostate gland. The temperature, pulse rate and leukocyte count were within normal limits, and there was moderate secondary anemia. A flat plate was taken of the abdomen, which revealed a typical colonic pattern and a colonic type of distention. A barium sulfate enema was administered, but the barium did not pass beyond the rectosigmoid juncture. An attempt was made to give a 2 quart (1.8 liter) enema, but the patient was able to take only about a pint (0.9 liter). About an hour later a second 2 quart enema was administered, and at this time there was a sudden rush of sound as the enema passed the obstructed point. After administration of the enema, of which the patient took approximately a quart, there occurred the passage of a large amount of gas, and this was followed by the passage of fecal matter. The abdominal distention rapidly disappeared. The patient was given 2 ounces (60 cc.) of liquid petrolatum by mouth and a 2 quart enema every four hours. Twenty-four hours later he appeared to be clinically well. After another twenty-four hours a barium sulfate enema was again administered, and this revealed a carcinoma of the rectosigmoid junction, which was removed after proper preoperative care.

*Comment.*—This represents the most common type of obstruction of the large bowel, in which there is a narrowing of the lumen by carcinoma of the rectosigmoid juncture. The narrow lumen is then obturated by fecal matter. This at times can be washed away by an enema, which transforms a complete colonic obstruction into a partial or chronic colonic obstruction.

CASE 3.—A white man aged 66 years entered the Cook County Hospital in February 1940. He stated that he had been perfectly well except for slight constipation until one week before admission. At this time he had considerable difficulty in having a bowel movement and gave himself several enemas, which were successful. Four days before admission he noticed cramping pains in the abdomen. These cramps came at three to four minute intervals; they were severe, and he attempted to pass gas but was unable to do so. He noticed no gurgles or other sounds. He tried to give himself enemas but was unable to do so and took castor oil, which did not come out but produced severe abdominal cramps. These were followed by considerable vomiting. His abdomen became more and more distended.

For four days before admission he had not passed any gas, nor had he had a bowel movement. He admitted losing considerable weight in the last year but did not know how much.

Physical examination gave entirely negative results for a moderate amount of emaciation. The abdomen was grossly distended to about 4 fingerbreadths above the xiphopubic line; the distention appeared to be still greater in the flank. There was a scar of an old herniorraphy on the left side. The percussion note was tympanitic throughout, and the hepatic dulness was obliterated. On auscultation



Fig. 6 (case 3).—Roentgen film of a complete colonic obstruction. Note that the pattern of gas follows the general pattern of the distribution of the colon. The patient had a carcinoma of the rectosigmoid juncture.

rushes of peristalsis with interspersed silent periods were easily audible. Rectal examination gave entirely negative results. A flat plate of the abdomen showed a typical colonic distribution of gas with great dilatation of the intestinal loops. An attempt was made to administer a barium sulfate enema, but the patient could not retain any of the barium. A quart (1.8 liter) tap water enema was tried, but the patient took less than a pint. He was given 2 ounces (60 cc.) of liquid petrolatum, and two hours later a second and a third attempt were made to give a 2 quart enema, but both were unsuccessful. The patient vomited several times during the intervening period. It was decided that this patient had a complete

colonic obstruction and that, therefore, emergency intervention was indicated. With local anesthesia, a typical McNealy cecostomy was performed.<sup>9</sup> It was noted that there was an enormous distended cecum, while the terminal portion of the ileum appeared to be completely collapsed. The cecostomy wound was opened twenty-four hours later and drained a large amount of gas. Forty-eight hours later the patient had a small bowel movement by rectum. He made an uneventful recovery, and approximately three weeks later the cecostomy closed.

*Comment.*—This is the type of condition which is referred to in the foregoing sections as complete obstruction of the colon. It presents an indication for emergency surgical treatment. It has been our experience that frequently a cecostomy is done for such a condition and the patient has a normal bowel movement a short time thereafter. This does not mean that the cecostomy has been performed in vain. Probably some of the edema around the tumor has been diminished with the relief of the pressure. The cecostomy stoma closes spontaneously, and we believe that the operation is in these cases a life-saving procedure.

CASE 4.—A white woman aged 64 was admitted to the Cook County Hospital in June 1939, complaining of cramping abdominal pains, vomiting, distention and complete obstipation for two days. She had always been perfectly well until the onset of the aforementioned symptoms. On further questioning she told us that she had heard loud rumbling sounds in the abdomen with each of these pains. On physical examination she did not appear acutely ill. The temperature was 99.6 F.; the pulse and respiratory rates were normal. The white blood cell count was 9,400 per cubic millimeter. Examination revealed muffled heart sounds and considerable cardiac enlargement. The abdomen was distended to approximately 5 cm. above the xiphopubic line. There was no tenderness or rebound tenderness at any point in the abdomen. It was tympanitic throughout, and the hepatic dulness was much diminished. Vaginal and rectal examinations did not reveal any significant findings. Auscultation of the abdomen showed rushes of high-pitched, obstructive peristaltic sounds at intervals of about one minute.

A flat plate of the abdomen revealed a typical distention of the small bowel. A diagnosis was made of obstruction in the small intestine without any evidences of strangulation. The cause was somewhat obscure, as there were no scars of previous operations on the abdomen. The patient was therefore treated conservatively. A Levine tube was introduced and connected with a Wangenstein type of suction apparatus, and intravenous fluid was administered. At the end of forty-eight hours the patient appeared considerably brighter. There were no evidences of dehydration or of strangulation. The peristaltic sounds were somewhat quieter but were still coming in rushes. The abdominal distention, however, had not abated. A second flat plate of the abdomen at this time did not reveal any reduction in the size of the intestinal loops. It was therefore decided to operate on this patient, as she was in good condition. Operation was done with spinal anesthesia. At the junction of the collapsed and distended loops a large mass was felt in the lumen of the intestine. This mass was presumably a large gallstone. It was pushed upward into the distended loop of intestine, and this permitted gas to pass on to the collapsed portion

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9. McNealy, R. W., and Lichtenstein, M.: Simple Technique for Cecostomy, *Am. J. Surg.* **36**:620-622 (June) 1937.

of the intestine. The mass was then pushed downward into the more normal intestine, and it was found possible to push it approximately 1 inch (2.5 cm.) beyond the point of the original obturation. A longitudinal incision was then made directly above the foreign body, and this body was extruded. It proved to be a large gallstone. The incision in the intestinal wall was closed in a transverse direction. The patient had an uneventful course for six postoperative days and then suddenly had a massive collapse of the lung followed by severe pneumonia, from which she died.

*Comment.*—The condition of this patient exemplifies those in the delayed group. The fatal outcome does not alter the surgical result but rather demonstrates that certain complications will follow even in patients who, one believes, are properly cared for. The patient had been given adequate preoperative care and was in splendid condition at the time of the intervention. Nevertheless, nothing could be gained by delaying the operation.

CASE 5.—A woman aged 28 was admitted to the Cook County Hospital on Oct. 12, 1939. She stated that she had been operated on three months previously for "acute tubal infection," and that the tubes had been removed. After the operation she had a slow convalescence, and there was a high fever for several weeks. Eventually she was discharged from the hospital but continued to have considerable vaginal discharge. On the day before admission she suddenly had severe abdominal cramps and (on questioning just before operation) admitted that they had been associated with gurgling sounds in the abdomen. She vomited a great deal but had had some passage of flatus and a small bowel movement. On examination the abdomen was found to be slightly distended and very tender, and it showed evidences of rebound tenderness, especially in the left lower portion. The temperature was 100 F. (rectal), and the leukocyte count, 16,000 per cubic millimeter. Vaginal examination revealed so much tenderness that no organs were palpable. The abdomen was entirely silent.

A tentative diagnosis was made of diffuse peritonitis probably originating from a ruptured pelvic abscess. The patient was sent to a medical service. The febrile condition continued and soon assumed a septic aspect. The abdominal distention increased and was not controlled by continuous suction. After three days surgical consultation was sought. The only finding different from those aforementioned was that the abdominal distention was slightly irregular. A flat plate of the abdomen was taken, and this (fig. 5) revealed a single distended loop, suggestive of a volvulus. The patient was operated on immediately with spinal anesthesia. At operation a gangrenous volvulus of 5 feet of jejunum and ileum was found, which had already perforated. The loop was exteriorized. The patient died on the second postoperative day.

*Comment.*—This case well illustrates the difficulty in differentiating late strangulated loop intestinal obstruction with peritonitis from bacterial peritonitis with secondary paralytic intestinal obstruction. The condition of the patient had been considered as a clear example of the latter type for three days. When she was first seen by one of us it did not appear in any different light, but we ordered a routine flat plate of the abdomen. This demonstrated the lesion immediately, and within one

hour the patient was prepared for operation. Had this routine roentgen film been taken three or even two days sooner this patient might have been saved.

CASE 6.—A white man aged 32 years entered the Cook County Hospital in October 1939. He stated that he had always been well until twenty-four hours before admission, at which time he suddenly had cramping abdominal pains occurring diffusely throughout the abdomen. The cramps were severe and caused him to become nauseated, and he vomited four or five times during the twenty-four hours before admission. The pain at no time localized to one area of the abdomen. He had heard no rushes or gurgles in his abdomen. He stated that he had had one small watery bowel movement since the onset of this severe pain. He noticed, however, that his abdomen in the last three or four hours before admission gradually became distended. His past history was entirely irrelevant. On physical examination he appeared acutely ill. The temperature was 101.6 F., the pulse rate 120 and the respiratory rate 126. The white blood cell count was 14,000 per cubic millimeter. The heart and lungs were entirely normal. The abdomen was distended 2 fingerbreadths above the xiphopubic line. It was tympanitic throughout, and there was a reduction in the hepatic dullness. There was absolutely no tenderness or rigidity. There was no rebound tenderness. The Rovsing, obturator and psoas signs were negative. Digital examination of the rectum gave entirely negative results, there being neither tenderness nor palpable masses. Auscultation of the abdomen revealed that it was remarkably silent, with only an occasional tinkle. No rushes were heard. A flat plate of the abdomen was taken and surprisingly showed distention of both the small and the large intestine. A small bubble of gas was visualized in the rectum. Although the roentgenogram was typical of ileus due to bacterial peritonitis or to an extra-abdominal lesion, it was believed more probable that the patient had an intestinal obstruction. In the complete absence of tenderness, rebound tenderness and rigidity, the patient was treated with Wangenstein suction and intravenous salt solution was administered. An attempt was made to pass the Miller-Abbott tube, but it passed the pylorus only with great difficulty. After twenty-four hours the patient appeared somewhat more ill than he had on previous examination. There was still no tenderness or rebound tenderness, but the temperature was now 103 F. and the white blood cell count 18,500 per cubic millimeter.

A second flat plate of the abdomen was taken, and this showed even greater distention than had been observed on previous examination. Both the small and the large intestine appeared to be filled with gas. Abdominal exploration was therefore decided on, and a right median incision was made. When the peritoneum was opened it was found that the cavity was filled with pus. The origin of this pus was a ruptured appendix. The appendix was removed, and it was found that both the large and the small intestine were grossly distended. The patient had a very stormy course; a severe wound infection developed, and an infection occurred in the cul-de-sac. But he eventually recovered.

*Comment.*—This patient shows the extreme difficulty sometimes encountered in differentiating between an intestinal obstruction and the ileus caused by peritonitis. The roentgenogram was diagnostic but was discounted because of the clinical findings and the complete absence of tenderness and rebound tenderness. We readily admit that this is a great rarity.

## GENERAL COMMENT AND SUMMARY

Intestinal obstruction remains a deadly disease in spite of a better understanding of its mechanism and lethal factors. Much of the resultant loss of life is due to lack of consideration of details in diagnosis or to delay. These are probably due chiefly to faults of omission, which can occur when seemingly every possible diagnostic effort has been made. The routine discussed obviates some of the errors of omission. It probably will tend to increase certain mistakes in judgment, as a formulation tends to instil confidence, which is often rudely shaken. Every case of intestinal obstruction remains a diagnostic problem which demands repeated careful examination and the most deliberate and mature consideration. During the last few years tremendous advances have been made in the treatment of intestinal obstruction. They demonstrate, however, the inadequacy of the present diagnostic methods. Fuller appreciation of the value of careful observation and readiness to change methods of treatment should lead to a further reduction in mortality. The uniform routine has its limitations when applied to a disease as varied as intestinal obstruction. We have, however, attempted to present such a routine as a general guide for the evaluation of the individual case. We have also attempted, in this manner, to suggest the necessity of careful history taking, the necessity of careful and repeated physical examination and the extreme necessity of using every method of diagnostic approach in the individual case. Our main contention is that there is no one treatment for intestinal obstruction and that most conservative methods, as well as operative intervention, may have an application in the same case or in different cases. There is a definite time, however, when conservative methods must be forsaken for operative intervention. This time must be determined by all of the diagnostic acumen which the surgeon can muster.

# PRIMARY CARCINOMA OF THE GALLBLADDER

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Physicians seldom consider carcinoma of the gallbladder a factor of much significance when advising patients with gallstones regarding their management. Repeated emphasis has made the members of the medical profession aware of the possibility of malignant growth developing in some other sites of the body in connection with certain types of lesions. For example, when the roentgenologist reports an ulceration on the gastric side of the pylorus in a person with ulcer dyspepsia, nearly every physician knows the implications as far as malignant growth is concerned. In contrast to this, persons with gallstones are rarely thought of as having or as likely to have a carcinoma of the gallbladder.

Five cases of primary carcinoma of the gallbladder have been observed in a year and a half, and 4 of these were observed within six months. There was only 1 case in which the presence of a malignant tumor was suspected preoperatively; in the other 4 cases the patients were all considered before operation to have benign disease of the gallbladder. It is undoubtedly true that the number of cases observed by one surgeon in this relatively short time has been far in excess of the expected number of cases from a statistical standpoint. However, a report of these cases is considered worth while, as the problem of malignant tumor of the gallbladder is unquestionably closely related to that of benign cholecystic disease. It is because of this relation between malignant and benign disease of the gallbladder that some of the points to be mentioned, although well known to nearly all physicians, will appear to deal with benign rather than with malignant disease of the gallbladder. When it is considered that between 8 per cent and 10 per cent of adults have gallstones, the importance of the proper concepts regarding the many problems of disease of the gallbladder cannot be overestimated.

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## INCIDENCE

Ewing,<sup>1</sup> Erdmann<sup>2</sup> and Kaufmann<sup>3</sup> have stated that carcinoma of the gallbladder is said to comprise 5 to 6 per cent of all cancers seen at postmortem examination. Kaufmann<sup>3</sup> estimated it to be present in 8 to 10 per cent of cases of cancer in females. Various authors have estimated that cancer of the gallbladder ranks fifth or sixth in frequency among cancers of the digestive organs. In a recent monograph on surgery of the gallbladder and the extrahepatic bile ducts, Cutler and Zollinger<sup>4</sup> stated that in the last five years there have been only 6 cases of proved primary malignant tumor of the gallbladder at the Peter Bent Brigham Hospital in Boston. Cooper,<sup>5</sup> in a comprehensive article published in 1937, stated that approximately 2,000 cases of cancer of the gallbladder had been reported in the literature up to that time.

In various reported series of surgically removed gallbladders the incidence of the disease has ranged from 0.5 to 6.5 per cent. It seems safe to say that the average incidence is about 2 to 3 per cent. Marshall and Morgan<sup>6</sup> of the Lahey Clinic, reporting on 1,336 cases of disease of the gallbladder observed from 1928 to 1937, gave the incidence as 1.4 per cent. Smithies<sup>7</sup> reported 23 cases, comprising 2.3 per cent of the gallbladders he had removed. Erdmann,<sup>2</sup> in his survey, found 15 cases of malignant tumors and reported the incidence as 6.7 per cent. Mayo<sup>8</sup> in reviewing 405 gallbladders operated on by himself found 5 per cent with malignant growths. MacCarty<sup>9</sup> surveyed 4,998 gallbladders and found 24, or 0.5 per cent, to be cancerous. At the Mayo Clinic,<sup>10</sup> 89 of 14,978 gallbladders routinely examined after surgical

1. Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1922, p. 693.

2. Erdmann, J. F.: *Incidence of Malignancy in Diseases of the Gall Bladder*, *Am. J. Obst.* **80**:618 (Dec.) 1919.

3. Kaufmann, E.: *Pathology*, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 2, p. 1002.

4. Cutler, E. C., and Zollinger, R.: *Surgery of the Gall Bladder and Extrahepatic Bile Ducts*, *Am. J. Surg.* **47**:185 (Jan.) 1940.

5. Cooper, W. A.: *Carcinoma of the Gall Bladder*, *Arch. Surg.* **35**:431 (Sept.) 1937.

6. Marshall, S. F., and Morgan, E. S.: *Carcinoma of the Gall Bladder*, *S. Clin. North America* **18**:687 (June) 1938.

7. Smithies, F.: *Primary Carcinoma of the Gall Bladder: An Analysis of Twenty-Three Proved Instances of the Disease*, *Am. J. M. Sc.* **157**:67 (Jan.) 1919.

8. Mayo, W. J.: *Malignant Diseases Involving the Gall Bladder*, *M. News*, New York **81**:1105 (Dec. 13) 1902.

9. MacCarty, W. C.: *The Frequency of Strawberry Gall Bladder*, *Ann. Surg.* **69**:131 (Feb.) 1919.

10. Judd, E. S., and Baumgartner, E. J.: *Malignant Lesions of the Gall Bladder*, *Arch. Int. Med.* **44**:735 (Nov.) 1929.

removal between 1910 and 1927 showed carcinoma. This is an incidence of 0.59 per cent. Judd and Gray,<sup>11</sup> in a survey of 22,365 gallbladders, found 15,422 with stones and 312 with carcinoma; 212 of the tumors were in the gallbladder itself and 100 in the ducts. This makes the incidence 1.4 per cent if one includes all the carcinomas and 0.9 per cent if one excludes the ductal cancers. Gray<sup>12</sup> mentioned that in recent years the incidence of carcinoma of the gallbladder at the Mayo Clinic has been decreasing, and he attributed this to earlier operation in cases of disease of this organ.

As to sex, Ewing<sup>1</sup> stated that cancer of the gallbladder is much more common in females than in males, the ratio being about 4 or 5 to 1. Kaufmann<sup>3</sup> stated that 90 per cent of cancers of the gallbladder are in females; Judd and Gray,<sup>11</sup> 74 per cent, and Marshall and Morgan,<sup>6</sup> 70 per cent. This is in direct contrast to carcinoma of the ducts, for which the proportion is much higher in males—about 50 per cent or more of carcinomas of the biliary ducts occurring in males, according to Marshall and Morgan.<sup>6</sup> The ratio of females to males in cases of carcinoma of the gallbladder is analogous to the ratio of females to males in cases of benign disease of the gallbladder.

The age incidence also is similar to that of cancer elsewhere in the body. The tumors usually are found after the age of 40, about 60 per cent being seen between the ages of 50 and 60, although cancer has been reported at both extremes of life. Maxon, cited by Ewing,<sup>1</sup> reported the earliest age, 4 years, while the oldest patient was a woman aged 95, reported on by Kaufmann.<sup>3</sup> Thomas and Norica, cited by Ewing,<sup>1</sup> reported occurrence of the tumor in a woman aged 90.

#### ETIOLOGY: RELATION TO STONES

As with cancer elsewhere, the cause of cancer of the gallbladder is unknown, but nearly all writers give as the most probable cause an irritative factor based on the relation of calculi to carcinoma. Ewing<sup>1</sup> gave as the *modus operandi* the following: "Mechanical irritation of calculi, the peculiar form of lipid metabolism (cholesterin) and the irritative and digestive action of bile seem to combine in producing the remarkable susceptibility of this mucous membrane to cancer." Obviously there are other factors present besides stones, because most patients with gallstones do not have cancer. The role of stones as an exciting factor, however, seems definite. In rare cases adenomas of the

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11. Judd, E. S., and Gray, H. K.: Carcinoma of the Gall Bladder and Bile Ducts, *Surg., Gynec. & Obst.* **55**:308 (Sept.) 1932.

12. Gray, H. K.: Squamous Cell Epithelioma of the Gall Bladder and Liver, Cholecystectomy and Partial Hepatectomy: Report of a Case, *S. Clin. North America* **14**:717 (June) 1934.

gallbladder may become malignant. Such cases have been reported by Wellbrock<sup>13</sup> and by Marshall and Morgan.<sup>6</sup>

Stones have been found in from 60 to 100 per cent of all cases of cancer of the gallbladder, the figure varying as given from different sources. Kaufmann<sup>3</sup> gave the occurrence of stones as 96.7 per cent; Marshall and Morgan,<sup>6</sup> as 80 per cent, and MacCarty,<sup>9</sup> as 64 per cent. Ewing<sup>1</sup> stated that approximately 4 to 10 per cent of all patients with stone eventually have cancer. Marshall and Morgan<sup>6</sup> stated that in cases of carcinoma of the bile ducts the presence of stones in the gallbladder or in the ducts is not nearly so frequent, occurring in less than one half the cases.

It has been suggested that stones are the result rather than the cause of primary carcinoma of the gallbladder. This seems rather unlikely, for the following reasons: 1. There is usually a history of definite gallbladder colic of several years' duration. 2. Stones removed from gallbladders which have primary malignant growths appear of the "old" variety, as they are firm and usually of moderate or large size. Soft stones and sand are usually not seen, unless in conjunction with the aforementioned variety of stones. 3. Secondary carcinoma of the gallbladder is not nearly so frequently associated with stones. One might argue in this instance that the secondary malignant tumor does not involve the mucosal surface of the gallbladder but affects the serosal surface primarily. 4. In cases of stasis of bile in the gallbladder as the result of malignant tumor in the common duct or in the head of the pancreas, the incidence of stones is about the expected incidence for persons in the age group affected. Marshall and Morgan<sup>6</sup> stated that 4 of 50 carcinomas of the head of the pancreas were associated with gallstones.

#### SYMPTOMS AND SIGNS

The symptoms of this disorder as a rule are those of chronic cholecystic disease with stones. Pain in the right upper abdominal quadrant seems to be the most outstanding symptom; it is followed by jaundice, indigestion, loss of weight and colic. Pain and jaundice are the two symptoms most frequently seen, one or the other usually being given as the chief complaint. The pain is severe; it is that of gallbladder colic, and it assumes the same typical distribution. It has no relation to the taking of food and usually requires morphine for relief. It is the rare case in which jaundice occurs without pain. After the appearance of jaundice few patients live longer than six months. Other symptoms of indigestion, such as belching, bloating and water brash, are usually

13. Wellbrock, W. L. A.: Adenoma of the Gall Bladder, *Am. J. Surg.* 23:358 (Feb.) 1934.

associated with pain or jaundice. Loss of weight occurs as a late symptom. Not uncommonly the liver is palpable well below the costal margin, and a firm, irregular mass may less frequently be felt.

#### DIAGNOSIS

The diagnosis is made for the most part either at operation or during routine laboratory examination of the removed gallbladder. It is rarely made preoperatively, as most of the patients are thought to have chronic disease of the gallbladder with stones. The occasional patient suspected of having the disease preoperatively may have a large hard mass in the right upper quadrant of the abdomen, below the costal margin, or painless jaundice with loss of weight and anemia. The diagnosis, however, is most difficult to make; therefore, one must depend on operation or the laboratory data. Roentgen examination is of little help in establishing the diagnosis of cancer, although it usually indicates disease of the gallbladder by showing either actual stones or disturbance in function. However, Kirklin<sup>14</sup> mentioned a case reported by Taterka in which the cholecystogram was pathognomonic of carcinoma.

#### TREATMENT

The treatment in most cases depends on the findings at operation. In many cases abdominal exploration and removal of a specimen for biopsy constitute the only feasible procedure. In exceptional cases, such as that reported by Judd and Baumgartner,<sup>10</sup> a cholecystectomy with resection of the involved portion of the common duct has been carried out. Gray<sup>12</sup> has described a case in which he removed a portion of liver adjacent to the involved gallbladder. Webber<sup>15</sup> has suggested that the grade of malignancy as determined by frozen section at operation may guide the surgeon as to the correct procedure. He suggested that nothing radical should be done for tumors of the higher grades of malignancy. Choledochostomy above the involved segment of duct may be performed as a palliative procedure to relieve jaundice. In the cases in which I have operated choledochostomy appeared of questionable value, although there was usually a temporary improvement in the jaundice with its distressing pruritus.

Certainly when the diagnosis is in doubt operative intervention is indicated, provided the general condition of the patient permits. It is indicated because the diagnosis cannot be established as a certainty without such a procedure, and if too conservative an attitude is assumed

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14. Kirklin, B. R.: Cholecystographic Diagnosis of Neoplasms of the Gall Bladder, *Am. J. Roentgenol.* **29**:8 (Jan.) 1933.

15. Webber, I. M.: Grades of Malignancy in Primary Carcinoma of the Gall Bladder, *Surg., Gynec. & Obst.* **44**:756 (June) 1927.

by the surgeon, benign disease of the biliary tract, particularly stones in the common duct, may be missed. Something curative may be done in exceptional cases.

#### PATHOLOGIC PICTURE

There are three main types of carcinoma of the gallbladder: the adenocarcinoma, the squamous cell carcinoma and the mixed adenocarcinoma and squamous cell carcinoma. The first type mentioned is the most common and the second type the least common. Squamous cell carcinoma is assumed to represent a metaplasia of the mucosa of the gallbladder.

Adenocarcinoma is divided into three main types, according to Ewing:<sup>1</sup>

1. The villous, papillomatous or fungating type. This grows from the mucosal surface, eventually distends and obliterates the bladder and forms a bulky, well circumscribed tumor. This type of neoplasm is rarely seen early but may appear as fragile, villous or warty growths invading the gallbladder cavity. Rarely it may grow into the ducts. It may cause hemorrhage and usually produces thickening in the wall of the gallbladder. It tends to attack the surrounding tissues, especially the liver, although it may invade any tissue in close proximity to the gallbladder. In the greatest number of cases stones are found embedded in the mass. This type of tumor is found for the most part near the neck of the gallbladder.

2. The gelatinous type of malignant growth. This forms bulky tumors which infiltrate the wall, fill the cavity of the gallbladder and extend early to the liver, lymph nodes and peritoneum. This type is very rare.

3. The diffuse flat infiltrating carcinoma which begins as a sub-mucous growth or as a thickening or ulceration in the mucosa which has been the seat of chronic inflammation. It invades the wall early, and the gallbladder becomes thick and contracted. It extends to the liver early and may run its course as a secondary hepatic carcinoma in a fair number of cases. In the majority, however, it converts the gallbladder into a hard contracted mass without increase in bulk or constricts it into an hourglass form and fuses it with the adjacent viscera. This type extends early to the surrounding organs (liver, stomach, duodenum and colon), to which it is usually bound by adhesions along which the malignant growth tends to extend. This type may also by direct extension encroach on the ducts and is by far the most common variety seen.

In speaking of the structure of the malignant tumor, it is probable that the markedly scirrhous character of many early cancers of the gallbladder results from the chronic inflammation preceding the new growth, as this is often found in cases of chronically diseased gallbladders with

stones in which there are noted blunt or nodular plaques 2 to 5 mm. in diameter which microscopically show foci of cellular connective tissue surrounding groups of typical glandular epithelium undergoing mitosis. These eventually produce adenocarcinoma of the gallbladder.

#### CLINICAL AND LABORATORY DATA

There were 5 cases. Four of the patients were women, and 1 was a man. The ages were 52, 62, 62, 69 and 70, with an average age of 63. The duration of symptoms referable to the gallbladder in 4 cases was thirty, eight, five and four years, respectively. In 1 case there were no

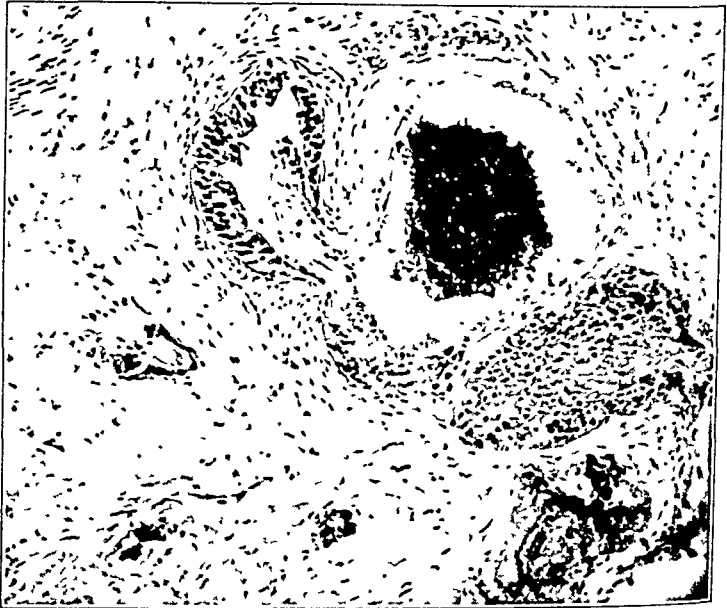


Fig. 1.—Low power photomicrograph of tissue removed from the cystic duct portion of the gallbladder at the second operation. (High cholecystectomy was done for empyema with stones nine months previously, and the gallbladder tissue removed at that time was only inflamed.) The section shows aberrant glandular structures in a dense stroma. Dark-staining calcareous material is present in the lumen of one of the glands.

antedating symptoms referable to the gallbladder (symptoms present for one month only). Rapid loss of weight and jaundice had been observed for one month. In 2 cases there was considerable loss of weight; in the first, 40 to 45 pounds (18 to 20 Kg.) was lost in eight months, and in the second, 20 pounds (9 Kg.) in one month. Slight anemia was present in only 1 case, the value for hemoglobin being 78 per cent. Jaundice was present in all cases at varying times. In 3 cases there was no palpable mass except that representing moderate enlargement of the liver. Cholecystograms in 3 cases showed a nonfunctioning gallbladder

and in 1 case gallstones. In the fifth case only a flat plate of the abdomen was taken on account of the intense jaundice. No stones were visualized in this case. The preoperative diagnosis in 4 cases was gallbladder stones and in 1 case was malignant tumor of the biliary duct.



Fig. 2.—High power photomicrograph of the acinus which is shown in upper left of figure 1. The section shows a pseudostratified arrangement of columnar epithelium, hyperchromatic nuclei and mitotic figures. There are loss of polarity of the nuclei and desquamated cells in the lumen.

The pathologic diagnosis of tissue removed from the gallbladder or of a segment of the gallbladder was adenocarcinoma in all 5 instances (figs. 1, 2, 3 and 4). The duration of life subsequent to primary operation in 4 cases was thirteen months, nine months, six months and seven

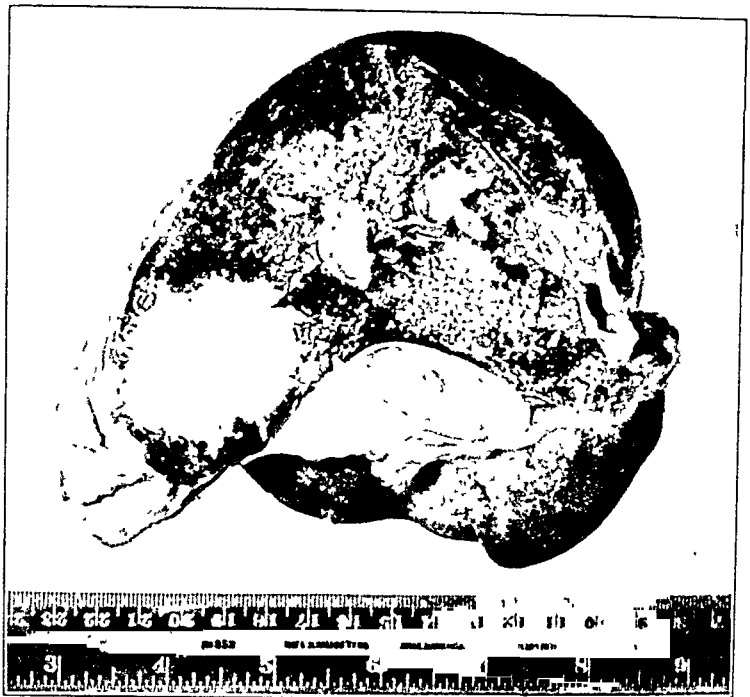


Fig. 3.—Cut surface of the liver at postmortem examination, showing a large carcinomatous nodule in the liver, adjacent to the gallbladder fossa (same case as figures 1 and 2).



Fig. 4.—Low power photomicrograph of liver at autopsy (fig. 3) showing irregular glandular structures in the upper part and liver cell columns in the lower portion. There is the same tendency to a scirrhous type of structure as was seen in the primary lesion, but not as marked. Endothelial cells containing brown pigment are present at the upper right. The clear vacuolated areas represent degenerated liver cells.



months, respectively. One patient died one week after the operation of renal insufficiency. The average duration of life of patients who survived immediate operation was nine months. The mortality was 100 per cent.

#### OPERATIVE PROCEDURES

Two patients were operated on once. On 1 of these cholecystectomy was performed; on the other cholecystectomy and choledochostomy.

Three patients were operated on twice. Two of these underwent primary high cholecystectomy for empyema with stones. The gallbladder tissue removed at this operation showed no evidence of malignant tumor. Reoperation in each instance revealed carcinoma in the stump of the gallbladder. A choledochostomy was done in each instance. The third patient underwent primary cholecystectomy and choledochostomy. Several weeks later a secondary operation was undertaken, but the wound was simply closed after exploration, since palliative choledochostomy was technically impossible.

#### OPERATIVE FINDINGS AND DIAGNOSES

Stones were present in all cases and empyema in 3 cases. In 1 case the patient had a single stone, which was "silent." The diagnosis of cancer by frozen section was made at the operating table in only 2 cases. In the third case carcinoma was observed in the removed gallbladder. In the 2 other cases, in which operation was done for presumed simple empyema and a high cholecystectomy performed, there was subsequent recurrence of symptoms, with jaundice. At reoperation the patients in these 2 cases had primary malignant tumor of the stump of the gallbladder with involvement of the ducts. It is believed in retrospect that malignant tumor was present in the cystic duct portion of these 2 gallbladders at the time of the original operation.

#### COMMENT

From the history and operative findings in all cases it is undoubtedly true that gallstones antedated the formation of carcinoma in each case. In 3 cases there was superimposed empyema. Involvement of the cystic duct end of the gallbladder with cancer may have caused the empyema in these cases. In every case except 1 the patient had seen a physician several years before for attacks which should have made the diagnosis clear. One patient had undergone roentgen examination about three years prior to operation, which revealed stones. In no case, according to the patient's story, was the patient urged to be operated on prior to the operation performed by me. One patient had been treated symptomatically for years by the family physician.

While, perhaps, one could not argue too strongly for operation on the gallbladder in any case of gallstones on account of the possibility of malignant tumor developing later, there are some other justifiable bases for early operation: (1) to prevent the distress of recurrent colic and dyspepsia; (2) to avoid stone in the common duct with infection and hepatic damage, and (3) to prevent remote visceral degenerative changes. It seems that the possibility of carcinoma could be given as a fourth reason for early operation in such cases.

While early operation on young persons with small stones or even on older persons in whom a stone in the common duct may be missed may result in postoperative colic or even in the necessity of a secondary operation, it seems that early operation has much more to offer than any type of medical treatment. Before early operation is advised in any case, the importance of an accurate diagnosis cannot be over-emphasized. It is believed that a history of typical colic is the most important single factor, but in addition there are the physical findings, the laboratory data and particularly the cholecystograms.

It must be borne in mind that there are some cases in which the cholecystogram may be misleading. In some cases, particularly when small stones are present, it may be reported that there is a normally functioning gallbladder without stones. Again, a nonfunctioning gallbladder may be reported in certain cases, particularly of persons who are neurotic and have a low basal metabolic rate. Often, if such a patient is operated on without an adequate history of gallstones, the gallbladder will be found normal anatomically, and the patient will not be relieved by cholecystectomy.

Persons suffering from migraine, chronic nervous exhaustion, chronic constipation and certain functional states, as well as certain organic diseases (which may be either extra-abdominal, such as coronary disease or tabetic crisis, or intra-abdominal, such as the perforating type of peptic ulcer), must be carefully considered in the differential diagnosis.

It seems that unless the patient has some other severe complicating disease operation is clearly indicated. It is surprising how well some persons with some types of complicating severe organic disease stand operations on the gallbladder. Medical treatment with diet, cholagogues, duodenal drainage and the like should be reserved for persons who refuse operative treatment. The risk of a well performed cholecystectomy is about 2 per cent, which may be regarded as about equal to the possibility of development of malignant tumor.

Graham<sup>16</sup> stated that 4 to 5 per cent of women of the cancer age who have gallstones will have carcinoma of the gallbladder and that the

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16. Graham, E. A.: The Prevention of Carcinoma of the Gall Bladder, *Ann. Surg.* **93**:317 (Jan.) 1931.

risk of cholecystectomy is only 1.5 per cent. Hence he expressed the belief that cholecystectomy can justifiably be advised on this basis alone. When one considers other undesirable conditions which patients with gallstones may have or acquire operation certainly is most often the procedure of choice. Among persons who have "silent" stones and later have cancer of the organ there will be necessarily a large percentage in whose cases the malignant growth is unavoidable, since the condition has been entirely asymptomatic until the development of malignancy. However, there will be a certain percentage of patients in whom gallstones are discovered accidentally, i. e., during the course of a pelvic or abdominal operation or during roentgen study.

It seems that advice based on all the clinical and laboratory data available should be given to the individual patient. It is believed that operation will be indicated in most cases of gallstones even of the so-called "silent" variety. Indeed, can one say how long such stones will be "silent?"

Hochberg and Kogut<sup>17</sup> stated that cancer may not be formed by stones but that the same agent or factor in the mucous membrane of the gallbladder which causes stone may be a factor in causing cancer. Be that as it may, from a clinical standpoint stones seem to antedate the carcinoma by some time, and if the cholelithiasis were managed adequately and early it seems that carcinoma of the gallbladder could be prevented in most instances. Some cases of carcinoma of the gallbladder have been reported (Marshall and Morgan;<sup>6</sup> Cooper<sup>5</sup>) in which the gallbladder had been previously drained for stones. In some of these cases multiple drainage operation had been performed for stones, and 1 case was reported in which an interval of fifteen years intervened between the cholecystostomy and the operation which revealed carcinoma in the gallbladder. This would argue for cholecystectomy rather than cholecystostomy when conditions seem to justify such a procedure.

#### CONCLUSIONS

1. Most frequently the clinical picture of carcinoma of the gallbladder is similar to that of benign disease of the organ, and as a rule a definite diagnosis is impossible without the operative or pathologic data.
2. Most patients with carcinoma of the gallbladder have a history of gallbladder colic of some years' duration, stones being found in almost all cases.
3. The prognosis in most cases of carcinoma of the gallbladder is poor; few patients live more than one year after the diagnosis has been made.

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17. Hochberg, L. A., and Kogut, B.: Primary Carcinoma of the Gall Bladder, *Am. J. Surg.* 43:746 (March) 1939.

4. When malignant tumor of the biliary tract is suspected but cannot be proved, operation is justified because (1) some patients will have benign conditions readily amenable to surgical treatment and (2) in rare instances a curative procedure may be carried out even in a case of malignant disease, and frequently a palliative operation may be performed.

5. It is believed that for patients who are good surgical risks early operation for definite benign disease of the gallbladder and even in cases of so-called "silent" stone will reduce the frequency of cancer of this organ.

## REVIEW OF UROLOGIC SURGERY

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*(Concluded from page 452)*

### PROSTATE GLAND

*Perineal Prostatectomy.*—Davis<sup>27</sup> presented a tabulation of late results after perineal prostatectomy, based on an analysis of replies to questionnaires sent to 100 consecutive patients. Davis<sup>27</sup> was able to maintain a mortality rate of 2.7 per cent in a series totaling 831 consecutive cases of perineal prostatectomy at the time he reported. All the operations were done with the patients under sacral block anesthesia. However, of as great importance as the mortality rate is the matter of late functional results. Most of the men who undergo perineal prostatectomy are in the twilight of life and are interested primarily in comfort. Davis<sup>27</sup> thought it futile to save "a life not worth living (from the point of view of the patient himself) by reason of continued suffering."

In 100 consecutive cases the average age of the patient was about 68.5 years. The average amount of tissue removed was 56 Gm. The perineal wounds closed in an average of sixteen and one-half days, except

27. Davis, E.: *Technic and Results in Perineal Prostatectomy*, J. A. M. A. 115:582-584 (Aug. 24) 1940.

for two fistulas, which required secondary closure. The postoperative duration of hospitalization averaged twenty-one days. Fifteen patients thought that they urinated too often, and 2 said that they urinated with difficulty. Twenty patients did not have to urinate at night; 41 had to rise once; 33 rose from two to four times, and 6 rose more than four times. On the subject of incontinence 253 additional replies were added to the ones in this questionnaire, making a total of 353. Of these replies, 1 indicated that a patient had complete incontinence; 3 indicated that 3 patients had partial but definite incontinence, and 8 indicated that 8 patients had slight or doubtful incontinence. As judged by the patients' own opinions, 89 of them were well, 10 were improved and 1 was unimproved.

*Content of Hormones in Urine During Prostatic Enlargement.*—Dingemans and Laqueur,<sup>28</sup> discussing the content of hormones in the urine in the presence of prostatic hypertrophy, stated that for 13 of 16 patients suffering from prostatic hypertrophy the amount of comb growth-promoting substances excreted per day in the urine was less than 20 international units. In only 3 cases did the amount excreted in the urine reach 50, 44 and 50 international units respectively. The amount of estrogenic substances found in the same urine exceeded 20 international units per twenty-four hours in 1 case only. "The ratio I. U. estrogenic substances: I. U. comb growth substances varied between 0.4 and 2.2," the authors reported. In the absence of prostatic hypertrophy, the urine of 16 men more than 50 years old was examined, and in only 4 cases was less than 18 international units of comb growth substances found in twenty-four hour specimens of urine. In 3 cases the amount of estrogenic substance in the same length of time (twenty-four hours) was less than 40 international units, whereas in 9 cases it exceeded 100 international units. The average amount excreted in the 16 cases was 98 international units per twenty-four hours. In this group the ratio (in international units) of estrogenic substances to comb growth substances was 2 or more in 15 cases. Three patients who had carcinoma of the prostate gland were examined. None of the 3 excreted urine which had an increased content of sex hormones.

*Calculi.*—Henline<sup>29</sup> stated that many patients suffering from prostatic concretions are symptomless and require no treatment of any sort. When symptoms develop from infection or coexisting adenoma of the prostate gland, the severity of the symptoms or complications resulting

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28. Dingemans, E., and Laqueur, E.: The Content of Male and Female Hormone in the Urine of Patients with Prostatic Hypertrophy, *J. Urol.* **44**:530-540 (Oct.) 1940.

29. Henline, R. B.: Prostatic Calculi: Treatment by Subtotal Perineal Prostatectomy, *J. Urol.* **44**:146-168 (Aug.) 1940.

from the prostatic calculi should determine the necessity for treatment. Urethroscopic study and semilateral cystourethrograms may be helpful in determination of the best treatment to employ. Transurethral resection or a punch operation may afford temporary relief but may not cure the patient. Perineal prostatotomy, with removal of some of the calculi, may leave enough calculi to cause recurrence of symptoms or may result in an infected prostate gland, so that recurrence of symptoms would be initiated. Subtotal perineal prostatectomy was described by Henline<sup>28</sup> as a means by which calculi or an infected prostate gland and capsule may be cleanly and completely removed. Complete removal of all the infected glandular tissue with the calculi by subtotal perineal prostatectomy should eliminate the focus of infection and offer a permanent cure without complications. Urinary control was immediate after removal of the urethral catheter from 4 of the 5 patients mentioned by Henline;<sup>29</sup> the fifth patient required about two months to achieve complete control. Rectourethral fistula did not occur, and Henline<sup>29</sup> stated that with proper perineal dissection it should not be a complication.

*Carcinoma.*—On the basis of a statistical analysis of a series of 677 cases of prostatic carcinoma in which the patients were treated in different ways, Barnes<sup>30</sup> concluded that endoscopic resection of the neck of the bladder is the treatment of choice for symptoms of obstruction and that the subsequent use of roentgen rays has a tendency to postpone recurrence of the growth. The latter opinion, he thought, is substantiated on examination of patients who have lived a year or two after high voltage roentgen therapy and do not show any clinical evidence of carcinoma. Because of these observations it is possible that when the patients more recently treated have been followed for a longer period than at present results of statistical analysis will be more favorable to the patients who underwent transurethral resection followed by roentgen therapy. In this study no patients had undergone total radical perineal prostatectomy. In a comparison of the data on this operation as reported by others with the data presented by Barnes,<sup>30</sup> there is a significant difference in favor of total prostatectomy over any other form of treatment.

*Infarction.*—Hubly and Thompson<sup>31</sup> reported 3 cases of prostatic infarction studied as to gross and microscopic pathologic aspects and as to the mechanical effects of the lesion as it affects the function of the posterior portion of the urethra. In case 1 there was an early infarction. The authors discussed the experimentally produced volumetric changes

30. Barnes, R. W.: Carcinoma of the Prostate: A Comparative Study of Modes of Treatment, *J. Urol.* **44**:169-176 (Aug.) 1940.

31. Hubly, J. W., and Thompson, G. J.: Infarction of the Prostate and Volumetric Changes Produced by the Lesion, *J. Urol.* **43**:459-467 (March) 1940.

in other organs. In case 2 two infarctions may have been present, one rather recent and the other having occurred four years prior to the time of the report. In case 3 multiple infarction was present, with healing by formation of fibrous connective tissue, subsequent contraction and no regeneration. Causes of infarction may be distortion of the vascular supply by adenomatous hyperplasia (Abeshouse), protection against dispersion of local infection, that is, prostatitis (Wilensky), arteriosclerosis, thrombophlebitis or circulatory stasis. The symptoms depend on the mechanical effects, size and age of the infarction.

*Sarcoma.*—Stevens and Barringer<sup>32</sup> reported on the records of 16 patients who had had prostatic neoplasms diagnosed either clinically or microscopically as sarcoma. The authors included 3 cases of anaplastic carcinoma because it is so readily confused in its history, physical examination and histologic aspects with sarcoma. In 4 cases the initial diagnosis was abscess, and in these cases the prostate gland was explored for pus. Of 5 growths proved microscopically to be myosarcomas, 3 had been diagnosed primarily as benign hypertrophy, and the patients had been subjected to prostatectomy. There were 1 spindle cell sarcoma and 1 lymphosarcoma. In the remaining 6 cases the lesions were regarded clinically as sarcomas. Stevens and Barringer<sup>32</sup> suggested a pathologic classification of only four types, based on the origin of the tumors: (1) myosarcoma, (2) lymphosarcoma, (3) sarcoma of indeterminate origin and (4) anaplastic carcinoma. The literature was reviewed for opinions and examples, particularly in discussion of the histories and courses of patients who had different types of sarcoma of the prostate gland. The less malignant sarcomas (and especially myosarcoma) may suggest benign hypertrophy in older men, who, accordingly, should be subjected to prostatectomy. Sarcoma is most malignant when it affects young persons, and the diagnosis may be suggested by the early age of the patient, the brief history, the increased size of the prostate gland, the elasticity and perhaps the irregularity of contour of the gland without induration, the presence of a suprapubic mass connected with a prostatic tumor and, sometimes, the rapid loss of weight and the presence of cachexia.

Differential diagnosis must be made to exclude abscess, calculus, cyst or carcinoma of the prostate gland, large tumors of the bladder and retrovesical sarcoma. Formation of such a diagnosis is aided by the use of an aspiration needle and by the roentgen ray therapeutic test, as well as by employment of the usual urologic instruments and methods. In practice, Stevens and Barringer<sup>32</sup> wrote, they recognize two groups of cases: first, those in which diagnosis is not made until after prostatec-

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32. Stevens, A. R., and Barringer, B. S.: *Sarcoma of the Prostate*, *J. Urol.* 44:83-108 (July) 1940.



tony for supposed hypertrophy has been done and in which usually a tumor of a low degree of malignancy is actually present; second, those in which unusual and large tumors of high malignancy are present. The experience of the authors and the literature both demonstrate the superior value of irradiation over that of surgical procedures.

Counseller and Bedard<sup>33</sup> reported on 4 patients suffering from sarcoma of the prostate gland who were encountered between 1925 and 1938. In all, 9 such patients have been encountered at the Mayo Clinic, 5 of whom were reported on previously by Bumpus. Of the 4 patients reported on by Counseller and Bedard,<sup>33</sup> the first had a fibrosarcoma; the second probably had a rhabdomyosarcoma; the third had a lymphosarcoma, and the fourth had a leiomyosarcoma. Histologic evidence was presented in support of these diagnoses. In the authors' experience, the treatment of choice for sarcoma of the prostate gland is prostatectomy followed immediately by radium and roentgen therapy.

#### BLADDER

*Tumors.*—Ash<sup>34</sup> stated that more than 3,200 cases of epithelial tumors of the bladder are recorded in the Bladder Tumor Registry of the American Urological Association. The pertinent clinical data can be summarized as follows: More than three times as many males as females are affected, and this proportion has been maintained consistently through the years in an increasing number of cases. Age is definitely significant; more than 80 per cent of the tumors occurred in patients more than 50 years of age. There are no epithelial tumors which appear in the first decade, and such tumors are rare before the fourth decade. The youngest patient in the registry was a youth 17 years old at the onset of symptoms; the youngest female patient was a woman 27 years old, but there was some question as to whether her tumor was primary in the bladder. Practically 15 per cent more females than males treated are living without tumor; correspondingly, a similar percentage of males (that is, over females) have either died of tumor or have had recurrence. Hematuria was the primary symptom in about 75 per cent of the cases, dysuria frequently being an associated symptom. More than two thirds of the tumors were situated in the most physiologically active part of the bladder—the posterior wall, including the trigon and the neck. Tumors on the anterior wall were not common. Tumors of the vault are of importance, despite their small incidence, because they are more likely to metastasize than are those in other parts of the bladder. It is probably true also that, since they are situated in a less active portion of the

33. Counseller, V. S., and Bedard, R. E.: Sarcoma of the Prostate Gland, *J. Urol.* **43**:836-843 (June) 1940.

34. Ash, J. E.: Epithelial Tumors of the Bladder, *J. Urol.* **44**:135-145 (Aug.) 1940.

bladder, such tumors do not reveal themselves clinically as early as do other tumors and may therefore be more extensive before they are treated.

Judged by ordinary criteria for malignancy, especially metastasis, tumors of the bladder are comparatively benign, but, like papillomas of the larynx, occurring as they do in an important physiologic part, they lead to such serious complications that they are far from benign clinically. More than 50 per cent of patients who had such tumors are dead, yet only about 12 per cent of the entire group of patients suffered from metastasis. In the registry the term "death with tumor" is used advisedly, because the great majority of patients registered did not die of the tumor but of some complicating condition, such as (most frequently) ascending infection of the urinary tract. If the real nature of all the tumors could be determined, it probably would be found that 80 to 90 per cent of them started as papillary tumors. Papillary tumors of the bladder are consistent. Specimens taken from different parts of the same tumor or specimens taken from multiple tumors or from tumors recurring in the course of years may run consistently to type. In conclusion, Ash<sup>34</sup> constructed the following "average case" from the statistics in the registry: The patient is a white man aged 60. The chief complaints are hematuria and dysuria. Cystoscopic examination reveals a single papillary tumor located on the posterior surface of the base of the bladder. Pathologic study reveals papillary carcinoma, grade I or II. The prognosis is repeated recurrence in spite of treatment; the patient has about one chance in three of living five years and about one chance in twenty-five of complete recovery.

Colby<sup>35</sup> stated that there is little evidence to support the contention that malignant tumors of the bladder can be cured by supervoltage irradiation; he discussed the subject from the position of the question whether the tumors really are affected by such treatment. The method is recent, and dosage is still unstandardized. In the group of cases which Colby<sup>35</sup> studied the cancer seemed to have been affected to a greater extent by supervoltage treatment than by other forms of external irradiation with which Colby<sup>35</sup> was familiar. Extensive tumors have regressed to the point of gross disappearance, but there is evidence that even in such a favorable event cancer cells persist in the deep layers of the wall of the bladder. Although the intravesical portions of a tumor may disappear, large portions of cancer can persist in the deep structures and then reappear in the bladder. Such recurrent cancers have responded less well to additional irradiation, and in no instance has the tumor disappeared again after more treatment. The most favorable

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35. Colby, F. H.: Supervoltage Radiation in the Treatment of Bladder Tumors. *J. Urol.* **44**:216-222 (Aug.) 1940.

results have been obtained with patients who had received no previous treatment. Colby's<sup>35</sup> experience during the two years prior to the time of his writing led him to the conclusion that this treatment should be used only for patients suffering from advanced tumors or for old and debilitated patients and that any tumor of the bladder suitable for surgical treatment should be operated on.

Thompson and McDonald<sup>36</sup> reported a case of neurofibroma of the urinary bladder. They stated that neurogenic tumors arising in the genitourinary organs are exceedingly uncommon. They referred to the literature, in which only 3 cases of neurogenic tumor of the bladder are reported. The patient in their own case was a man 59 years old. He had a tumor about the size of a grapefruit which presented between the bladder and the rectum and which could be palpated on rectal examination. The bladder was surgically explored suprapubically, and a large cystic growth was encountered. It was attached to the bladder, near the prostate gland. It was removed and on histologic examination was found to have the typical characteristics of neurofibroma. The immediate postoperative convalescence was uneventful. Sixteen months later the patient was in good health and showed no evidence of recurrence of the tumor.

*Carcinoma with Exstrophy.*—McCown<sup>37</sup> discussed carcinoma associated with exstrophy of the bladder and added to the scant literature on this subject a case of adenocarcinoma, with complete details and the observations made at necropsy. He reviewed 24 additional cases which he obtained from the literature. In 9 of these 24 cases the treatment was symptomatic or supportive, because of the grave condition of the patients. Four of these patients underwent transplantation of the ureters with excision or extirpation of the neoplasm. Of these 4 patients, 1 died three years later, of metastasis; 1 died within two years, of metastasis; 1 was working six months later, and 1 died on the eighth postoperative day, from ascending infection and uremia. One patient, who underwent extirpation only, was living fifteen months after operation. In 1 case exclusion of the rectum was attempted; the patient died. One patient treated by diathermy, ureterostomy, nephrectomy and cystectomy was recovering at the time of McCown's<sup>37</sup> report. One patient recovered from the Sonnenburg operation but was not traced. In 1 case the neoplasm was removed by electrocautery but recurred; the patient received roentgen therapy and was well five months later. One patient was well three years after cautery excision of the bladder; 1 other patient was

36. Thompson, G. J., and McDonald, J. R.: Benign Tumors of the Urinary Bladder: Report of a Case of Neurofibroma, *J. Urol.* **43**:831-835 (June) 1940.

37. McCown, P. E.: Carcinoma in Exstrophy of the Bladder, *J. Urol.* **43**: 533-542 (April) 1940.

well six years and six months after excision of the tumor and application of radium. The best results were achieved by excision, irradiation or a combination of the two.

*Diverticulum.*—Dees<sup>38</sup> reported and analyzed 95 cases in which vesical diverticulectomy was carried out at the Brady Urological Institute of the Johns Hopkins Hospital. The most common symptoms were those of obstruction of the vesical neck. Infection of the urinary tract was present in all but 7 patients; in 69 of the remaining 88 patients this infection was very severe. The most common cause of obstruction of the neck of the bladder was either contracture of the vesical orifice or formation of a median bar. Slight or moderate prostatic enlargement caused by benign hypertrophy was the next most frequent cause. Transvesical diverticulectomy was carried out in 79 of the 95 cases; extravesical diverticulectomy or a combination of transvesical and extravesical diverticulectomy was done in the remaining 16. In all but 16 cases it was necessary to correct obstruction of the vesical neck in addition to performance of diverticulectomy. The great majority of postoperative complications encountered were caused by infections, epididymitis, pyelonephritis and infection of the wound being by far the most common of these.

In 50 per cent of the cases postoperative urinary drainage continued for more than forty days. Persistent prostatic obstruction was a relatively frequent cause of persistent drainage. Eight patients died in the hospital after the operation. The deaths of 5 of them were caused by pyelonephritis and uremia. The 87 surviving patients were followed for from six months to sixteen years. Of these, at the time of Dees's<sup>38</sup> report, 43 were living and cured; 6 were living and improved; 2 were living and not improved; 16 had died from unrelated causes, and 8 (of whom 5 had carcinoma of the bladder) had died of related causes within a year after operation.

*Vesicointestinal Fistula.*—Mayo and Miller<sup>39</sup> studied the records of 88 patients with sigmoidovesical fistula. The most common symptoms were frequency of urination, dysuria, chills and fever. Bubbles of gas often were passed through the urethra, usually at the end of micturition, but the passage of feces occurred less frequently. In the presence of a sigmoidovesical fistula the fecal content of the urine is dependent on the state of the stools; when they are firm and the patient is constipated, little or no feces will be seen in the urine; however, if the stools are loose, the quantity of fecal material in the urine will be increased. When the usual flow through such a fistula is reversed and urine is diverted

38. Dees, J. E.: Vesical Diverticulectomy, *J. Urol.* **44**:466-484 (Oct.) 1940.

39. Mayo, C. W., and Miller, J. M.: Surgical Treatment of Sigmoidovesical Fistulas, *Arch. Surg.* **40**:897-911 (May) 1940.

into the bowel, laxity of the bowels or chronic diarrhea may result. Cystoscopic examination is essential in formation of the diagnosis. Usually a fistulous opening, often on the left side of the bladder, may be visualized; however, at times this opening is obscured by a mass of granulation tissue or necrotic debris. Gas and occasionally feces may be seen bubbling through the fistula. When a suspicion exists that a fistulous tract is present but when a definite opening cannot be seen, a lead catheter can be passed gently through the suspected region and a roentgenogram made. The shadow cast by the catheter may then be seen in the colon. Force should not be used, because the possibility of creating a false passage thereby is definite. A cystogram may be of help in outlining the fistulous tract. Passage of methylene blue (methylthionine chloride) into the bladder after injection of it into the rectum, or vice versa, is conclusive proof that a fistula is present. Pyelitis and pyelonephritis are not common, despite the frequent occurrence of necrotic cystitis when a sigmoidovesical fistula is present. Mayo and Miller<sup>39</sup> found diverticulitis of the colon (sigmoid flexure) to be the most common cause of sigmoidovesical fistula. Less frequent causes were inflammation, carcinoma and trauma, in the order named. Most of the patients who had diverticulitis complicated by fistula were men (97 per cent), and the average age was 54.8 years. Men are affected more often than women because diverticulitis is more frequent among men. In women the uterus forms an effective barrier between the sigmoid flexure and the bladder. The treatment of choice generally is preliminary colostomy carried out at a site proximal to the lesion. An adequate amount of time should then elapse to permit spontaneous healing of the fistula. This type of healing will occur in certain cases. If healing does not occur, direct surgical attack on the fistula will be necessary. Drainage of the bladder by a suprapubic tube or an indwelling urethral catheter is advisable under these circumstances. Later the colonic stoma can be closed. Single stage operations directed toward excision of the fistula seldom are indicated.

*Vesicoappendical Fistula.*—Pemberton, Pool and Miller<sup>40</sup> stated that, although vesicointestinal fistula occurs but infrequently, the diagnosis and treatment of this type of fistula comprise one of the serious problems confronting the urologist and the surgeon. The majority of such tracts lead from the sigmoid flexure to the bladder and are the result of perforating diverticulitis of the sigmoid flexure, pelvic inflammatory disease (specific or nonspecific in origin) or carcinoma of the bowel. Kellogg found that the appendix was involved in 27 cases in a group of 592 cases of vesicointestinal fistula. Although variations referable to

40. Pemberton, J. deJ.; Pool, T. L., and Miller, J. M.: Vesico-Appendiceal Fistulas, *J. Urol.* 44:274-278 (Sept.) 1940.

the causative factor may be present, the general syndrome presented by patients suffering from vesicointestinal fistula is essentially the same. A history of distress, perhaps acute, in either of the lower abdominal quadrants usually is obtained. Simultaneously with such distress or later, burning and frequency of urination occur. Micturition may occur hourly, and it may be accompanied with scalding pain either during the act or at its completion. With the creation of a fistula, bubbles of gas may be passed through the urethra, and such passage usually occurs at the end of micturition, but the passage of feces does not occur so frequently as the passage of flatus. Cystoscopic study is invaluable in the diagnosis. With vesicoappendical fistula the opening usually is present on the right side of the bladder. Frequently the opening may not be seen, for a mass of granulation tissue or a depressed necrotic region in the bladder may be the only evidence that a fistula exists. When the presence of a fistulous tract is suspected, a lead catheter may be passed through the aperture and a substance opaque to roentgen rays may be injected. The resulting shadows may be seen to outline the fistulous tract and part of the colon.

Five patients who had vesicoappendical fistula have been seen and treated at the Mayo Clinic. Pyuria, varying in degree, was present in all cases. Cystoscopic examination revealed that 2 patients had diffuse inflammatory changes, and a third patient had the same changes (as those of the 2 just mentioned) present at the left base of the bladder. All patients underwent operation. Appendectomy and closure of the opening into the bladder were performed in 3 cases, resulting in 1 death from general peritonitis. Death also occurred in 1 of the remaining 2 cases.

*Vesicovaginal Fistula.*—Farsht<sup>41</sup> stated that the occurrence of vesicovaginal fistula of surgical origin is on the increase and that vesicovaginal fistula of obstetric origin is on the decrease. The fistula of surgical origin is, as a rule, fixed high in the vagina and is in close proximity to the ureters. The inaccessibility of this type of fistula by vaginal approach makes exposure, proper dissection and repair difficult. Good exposure, careful dissection of the fistulous tract, adequate mobilization of the vesical wall, separate suture of the vesical and vaginal orifices and proper preoperative and postoperative care are essential for successful repair of vesicovaginal fistula. The suprapubic transvesical method of approach allows proper execution of these principles, prevents unsuspected injury to the ureters and permits suprapubic drainage of the bladder, which Farsht<sup>41</sup> said is superior to other types of vesical drainage. This approach also is applicable to the majority of lower-lying fistulas which

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41. Farsht, I. J.: Suprapubic Transvesical Repair of Vesicovaginal Fistulas, *J. Urol.* **44**:279-300 (Sept.) 1940.

result from obstetric injury. An analysis is given of 20 cases of vesicovaginal fistula in which the patients were treated successfully, 3 by the vaginal route and 17 by the transvesical route.

*Cystitis Follicularis*.—Greene and Feldman<sup>42</sup> defined cystitis follicularis as a rare condition characterized by the presence of true follicles in the mucosa and submucosa of the urinary bladder. At times the renal pelvis and ureter may show similar involvement, and the disease is then designated as pyeloureteritis follicularis. The distinctive feature of this condition from the standpoint of pathologic aspects is the presence of sharply circumscribed lymph follicles which contain germinal centers and which differ in no wise from the solitary follicles of Peyer's patches. In the earlier literature the term "pyelitis granulosa" was applied to this condition. Four causative factors are mentioned in the literature; these are gonorrhea, syphilis, typhoid fever and tuberculosis. Greene and Feldman<sup>42</sup> reported the discovery of cystitis follicularis by cystoscopic study in a mature female dog. The trigon and base of the bladder were covered with small, grayish white nodular excrescences, each surrounded by a red peripheral zone. The nodules varied in diameter from 1 to 2 mm. and appeared to be solid. Gram's stain revealed the urine to contain an enormous number of gram-negative bacilli; growth on eosin, methylene blue and blood agar revealed a pure culture of *Escherichia coli*. Acid-fast bacilli were not found. Microscopically, sections of the bladder revealed lesions typical of cystitis follicularis.

Emmett<sup>43</sup> considered the problem of retention of urine resulting from imbalance of the detrusor urinae muscle and the vesical neck and recommended treatment by transurethral resection. Exclusive of definite prostatic enlargement, for which the treatment is suprapubic prostatectomy, perineal prostatectomy or transurethral resection, there are other causes of obstruction, which are known as "atypical." Retention is classed as atypical when it occurs in: (1) men too young to be suffering from prostatism; (2) men of the so-called prostatic age who seemingly do not have prostatic hyperplasia; (3) men who have so-called neurogenic bladders, in whom the retention is associated with injury or disease of the central nervous system or of the peripheral nerves, and (4) either young or old in whom the condition has existed throughout their lives, no definite cause ever having been found. In the cases of such men as those last mentioned the condition has been vaguely diagnosed and has been termed, variously and evasively, "congenital atony of the bladder," "atonic bladder," "cord bladder," "neurogenic bladder,"

42. Greene, L. F., and Feldman, W. H.: Cystitis Follicularis in a Dog, Arch. Path. 29:511-516 (April) 1940.

43. Emmett, J. L.: Urinary Retention from Imbalance of Detrusor and Vesical Neck: Treatment by Transurethral Resection, J. Urol. 43:692-704 (May) 1940.

"hypotonic bladder" and "urinary retention of indeterminate etiology." Emmett<sup>43</sup> pointed out that if the desire to void is absent, as it is in cases of *tabes dorsalis* and subacute combined sclerosis, the muscle fibers are overstretched and lose their tone and the detrusor urinae muscle is incapable of expelling the vesical content. Similarly, mild unrecognizable obstruction of the vesical neck or a hypertrophic internal vesical sphincter muscle or one that is unable to relax properly or to coordinate during the act of micturition can easily produce sufficient obstruction for a long period to cause vesical atony and the accumulation of residual urine. The problem of the case in which urinary retention is atypical, according to Emmett,<sup>43</sup> has in the past been attacked from the standpoint of the detrusor urinae muscle. He said that in the past the diagnosis of "atonic cord bladder" depended on the cystoscopic demonstration of: (1) reduction of expulsive force; (2) trabeculation of the bladder; (3) diminution in sensation, and (4) relaxation of the vesical neck, plus the cystometrographic finding of a "hypotonic bladder" and the demonstration of any neurologic lesion, the most common being *spina bifida occulta*. The real problem involved in these cases of urinary retention of obscure causation was said to be not that of measurement of the actual potential expulsive power of the detrusor urinae muscle, but rather, of comparison of its expulsive force to the resistance that must be overcome by the urine which flows through the vesical outlet. In other words, estimation of the "balance of power" between the detrusor urinae muscle and the vesical outlet seems to be the all-important factor. If the vesical musculature is "weak" or "atonic," whether from neurogenic or from non-neurogenic causes, the problem at hand may well resolve itself into one of weakening of the vesical neck sufficiently to enable the incompetent detrusor urinae muscle to expel the content of the bladder completely. Aside from the common conditions of well defined prostatic hyperplasia and carcinoma of the prostate gland, a vesical neck may become obstructive and may resist the outflow of urine under the following circumstances: (1) when the vesical neck is normal and the detrusor urinae muscle is weak; (2) when coordination fails to occur between the internal vesical sphincter muscle and the detrusor urinae muscle or when the internal vesical sphincter muscle is unable to relax when the detrusor urinae muscle contracts (*dysectasia*); (3) when hypertrophy of the internal sphincter muscle is present; (4) when inflammation with subsequent fibrosis produces fixation of the vesical neck or contracture of the vesical neck with or without the formation of a median bar; (5) when chronic inflammatory changes are present in the prostatic portion of the urethra, and (6) when there is found a small degree of prostatic hyperplasia that does not appear to be obstructive on cystoscopic examination. These conditions may be extremely difficult



to diagnose cystoscopically even when carefully looked for. In such cases Emmett<sup>43</sup> recommended surgical treatment by a transurethral approach. He stated that if true incontinence does not exist prior to operation in these cases, it will not occur afterward if the external sphincter muscle (compressor urethrae) is not injured at operation. The term "incontinence" must be considered carefully as used in such cases. True incontinence must be distinguished from the overflow type of incontinence. For patients who have the overflow type of incontinence, transurethral resection is the procedure of choice, because this procedure is accompanied with practically no risk to the patient's life. It should be emphasized that transurethral resection must be done completely or the results will be poor. It is not sufficient to remove only one or two pieces of tissue from the posterior vesical lip. In cases in which prostatic enlargement is not present, tissue should be removed from the entire circumference of the vesical neck, so that the internal sphincter muscle will be completely removed. If prostatic hyperplasia is present, as nearly complete a prostatectomy as possible should be carried out.

Emmett<sup>43</sup> then presented 8 representative cases, in which the patients concerned were divided into four types. Under type A were listed patients who had had urinary retention during their entire lives, without any demonstrable neurologic lesion or obstruction of the vesical neck that would account for the retention. Under type B were classified patients who had urinary retention associated with a nonsyphilitic lesion or with injury to the central nervous system. Under type C were listed patients who had urinary retention produced by unrecognized obstruction of the vesical neck, such as contracture, and mild degrees of prostatic hyperplasia. Under type D were listed patients who had urinary retention associated with locomotor ataxia (tabes dorsalis). The functional result obtained in all cases reported in the entire series was excellent.

#### TESTICLE

*Tuberculosis.*—Thomas, Stebbins and Rigos<sup>44</sup> stated that tuberculosis of the testicle is not a primary condition and that it rarely occurs when no other genital lesion referable to this disease is present. They reported a case in which genital tuberculosis was localized in the testicle. Tests of the urine for gonadotropin are of value in the differential diagnosis of testicular enlargement. Tests of the blood for syphilis should be made to rule out gumma of the testicle. Aspiration and transillumination eliminate hydrocele and spermatocele. A Mantoux test should be conducted and roentgenograms of the thorax should be made in the presence of intrascrotal tumor. At operation an attempt should be made to

44. Thomas, G. J.; Stebbins, T. L., and Rigos, F. J. Tuberculosis of the Testicle, *J. Urol.* 44:67-73 (July) 1940

segregate the most strongly suspected tissues for microscopic examination, culture and guinea pig inoculation.

*Tumors.*—Gordon <sup>45</sup> made a study of the pathologic aspects of 142 primary tumors of the testis. Evidence was presented in favor of the hypothesis that essentially all neoplasms of the testis are of teratomatous origin, with cellular overgrowth of one germ layer often producing homogeneous neoplasms which resemble germinal epithelium. Careful search will reveal teratomatous remains in many characteristic neoplasms of this type, which cannot be distinguished microscopically from those in which teratomatous elements cannot be found. The occurrence of teratomatous elements exceeds the expected incidence or coexistence of two primary neoplasms in the same organ, and the investigator must therefore accept the teratoma as significant of the pathogenesis of tumors of the testis. No stages of transition between normal germinal epithelium and either embryonal carcinoma ("seminoma") or adenocarcinoma were found.

Gilbert <sup>46</sup> analyzed 129 cases of gynecomastia (mammary hyperplasia) associated with malignant testicular tumors. He added 6 cases of his own, thus arriving at a total of 135 cases. He subdivided this total into two groups: group 1 included 103 cases of gynecomastia associated with teratoid tumors, and group 2 comprised 2 of his own cases and 18 cases reported in the literature. Characteristics of the syndrome of choriogenic gynecomastia associated with tumors of the testis were said to consist of: chorionepithelioma in the primary or metastatic tumor; gynecomastia, usually bilateral, with hyperplasia of glandular tissue (often the only clinical symptom present); enlargement or hyperpigmentation (usually occurring together), of the areolas; physiologic activity manifested by either gross or microscopic demonstration of secretion in the breasts, high titers of chorionic gonadotropic hormones and the presence of estrogen; histologic changes in pituitary gland, described generally as "pregnancy cells," and, frequently, hyperplasia of the prostate gland or the seminal vesicles.

*Tumors in Mice Receiving Estrogens.*<sup>47</sup>—During the course of prolonged treatment with estrogenic substance, the glandular interstitial tissue of the testis in mice of the Strong A strain was observed to become hypertrophied, at times to such a degree that large portions of the testis

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45. Gordon, W. G.: Tumors of the Testis: A Study of the Pathology of One Hundred and Forty-Two Cases of Primary Neoplasms of the Testis in Man. *J Urol.* **43**:851-858 (June) 1940.

46. Gilbert, J. B.: Studies in Malignant Testis Tumors: II. Syndrome of Choriogenic Gynecomastia; Report of Six Cases and Review of One Hundred and Twenty-Nine, *J. Urol.* **44**:345-357 (Sept.) 1940.

47. Hooker, C. W.; Gardner, W. U., and Pfeiffer, C. A.: Testicular Tumors in Mice Receiving Estrogens, *J. A. M. A.* **115**:443-445 (Aug. 10) 1940.

were composed entirely of hypertrophied cells. Recently this change was observed to progress to such a degree as to produce a malignant tumor with metastasis. A mouse 30 days old received weekly injections of 0.05 mg. of estradiol benzoate. After six months the left testis began to enlarge rapidly, and after eight months it was several times normal size. When the animal was killed, the normal structures of the left testis were found to have been entirely replaced by a malignant tumor composed of cords and masses of large vacuolated cells which resembled the hypertrophied interstitial cells previously described. Metastasis to the lumbar and renal lymph nodes had occurred. Histologic changes in the accessory organs of reproduction indicated that these tissues were under the influence of androgenic substance, which suggested the possibility of endocrine activity of the hypertrophied and malignant cells. The right testis exhibited that type of hyperplasia usually seen after treatment with estrogenic substances, but no evidence of malignant tumor. A histologically similar testicular tumor which did not metastasize arose in a second mouse, of the same strain, which received stilbestrol.

*Congenital Absence.*—Counseller, Nichols and Smith<sup>48</sup> presented 7 cases of monorchia. Absence of the testicle occurred in 4 cases on the left side and in 3 cases on the right side. Study of the cases presented does not reveal any conclusive evidence as to the cause of this condition, nor does it reveal any diagnostic physical signs which will aid in distinguishing anorchidism from cryptorchidism. The importance of the surgeon's bearing this anomaly in mind when he is considering orchidopexy was discussed.

*Ectopia.*—Hunt<sup>49</sup> presented a case of bilateral ectopia testis pelvisis and discussed the causation, diagnosis and treatment of ectopia. If the testis is intra-abdominal and cannot be palpated, the diagnosis can be made only by operation. Failure of the examiner to make the diagnosis by exploratory operation with ectopia testis in mind probably has resulted in some cases in the incorrect diagnoses of single testis and atrophied undescended testis. The treatment of ectopia testis is surgical correction. In cases in which the true condition has been positively diagnosed by palpation, the operation should be done as soon as the patient has reached an age at which surgical intervention is safe. The intra-abdominally situated testis, which must be discovered by exploratory operation, presents a different problem as to the age at which operation is safe. Hunt<sup>49</sup> said that Johnson's analysis of 544 cases of undescended testes, in which the patients were boys who were prevented

48. Counseller, V. S.; Nichols, D. R., and Smith, H. L.: Congenital Absence of Testis: A Report of Seven Cases of Monorchidism, *J. Urol.* **44**:237-241 (Aug.) 1940.

49. Hunt, R. W.: Ectopic Testis: Report of a Case of Bilateral Ectopia Testis Pelvisis and Its Surgical Correction, *J. Urol.* **44**:325-332 (Sept.) 1940.

from having any treatment because of their economic standing, is enlightening in regard to this point. His studies showed that spontaneous descent occurs in about 15 of every 17 cases in which the patients are followed until they reach the age of 16 years and that such descent occurs at the age of 11, 12 or 13 years in three fourths of the cases. The patient who has intra-abdominal ectopia testis obviously belongs to the group comprising the 2 of 17 untreated patients who pass the age of 16 years without the occurrence of spontaneous descent; therefore, if the testis cannot be palpated and has not descended by the time the patient has reached the fourteenth year, exploratory operation should be done. The operation, to be satisfactory, must locate the testis and fix the gland in the scrotum without undue traction of the cord, and it must preserve the blood and nerve supply.

#### URETHRA

*Stricture.*—Riba and Harrison<sup>50</sup> discussed the association and incidence (10 per cent) of strictures of the male urethra and *Trichomonas vaginalis*. They reported 2 cases in which, in addition to strictures and trichomonads, intracellular diplococci were found. A damaged or chronically inflamed urethra with lowered resistance seems to favor the adaptation and local morbidity of trichomonads and to provide a source for dissemination of them.

#### URINARY LITHIASIS

The first part of Joly's report<sup>51</sup> on urinary lithiasis dealt with the origin and formation of urinary calculi. After a brief survey of the excretion of urine in the various groups of vertebrates, he pointed out that mammals alone excrete hypertonic urine. The concentration of the urine in these animals is undoubtedly a factor which predisposes to the formation of stone. Next, Joly<sup>51</sup> discussed the origin of stone-forming salts in the urine. He pointed out that all such salts exist in a state of supersaturation in the urine and that, although the solubility of these salts is profoundly modified by the  $p_H$  of the urine, the presence of other electrolytes and the peptizing action of urea, none of these factors is sufficient to account for the abnormal degree of solubility observed. The action of the urinary colloids was next discussed, and it was pointed out that the abnormal solubility of the stone-forming salts can be accounted for by the theory of adsorption. Adsorption means that the molecules of the sparingly soluble salts are attracted to the surface of the colloid particles and are held there. The effect of this

50. Riba, L. W., and Harrison, R. M.: Strictures of the Male Urethra and *Trichomonas Vaginalis*, Surg., Gynec. & Obst. **71**:369-371 (Sept.) 1940.

51. Joly, J. S.: The Etiology and Preventive Treatment of Urinary Lithiasis. Internat. Soc. Urol., Rep. (pt. 1) **7**:77-145, 1939.

process is that the solubility of such substances is greatly increased, whereas that of freely soluble salts is unchanged. Formation of a crystalline deposit in the urine occurs in persons in whom the protective action of the colloids is poor. The appearance of this deposit depends on whether it is formed in a colloid solution or in a watery solution. If the former, and if crystals are found in large numbers, it is probable that a stone will form. These forms have been observed in cases of experimental lithiasis, in patients suffering from stone and in the stones themselves. It is only when the stone-forming salts are deposited from, or in, a colloid solution that they can be built up into true calculi. The genesis of formation of stone probably is as follows: The first requisite is that some of the colloid must be precipitated in the form of a gel. The stone-forming salts are adsorbed to the surface of this gel, and crystals are deposited on it. As they form in and around the colloid mass, they take on the atypical form assumed by crystals arising in such a medium. Fresh colloid is deposited on this mass, and fresh crystals are formed on its surface. The laminated appearance of a calculus may be explained by the supposition that the deposition of colloid varies in a rhythmic manner, whereas the deposition of crystals is continuous and uniform.

The second part of Joly's <sup>51</sup> paper dealt with the causation of stone. The question of diet was first discussed, and it was shown that the incidence of stone is most common in districts in which the diet is poor, monotonous and ill balanced. Experimental evidence to suggest that stone may be caused by a deficiency of vitamin A was reviewed. It was also shown that clinical evidence of such deficiency frequently is found among the inhabitants of "stone areas" and that lesser degrees of this type of deficiency, which are recognizable only by means of the test for adaptation to darkness, are common in both England and America. Last, slight degrees of vitamin A deficiency have been recently observed in patients suffering from stone. The effects of infections of the urinary tract, of metabolic disorders and of either general or local diseases were next considered. Emphasis was laid on increased elimination of calcium salts in the urine in cases in which the patient is immobilized or suffers from injury or disease of bone or from hyperparathyroidism, and the relation of these conditions to phosphatic lithiasis was discussed. After a brief review of Randall's theory that stones arise from the "milk patches" occasionally found on the renal papillae, the relation of calculous disease to the uric acid infarcts of infants and the influence of renal anomalies on formation of stone were discussed. The geographic distribution of stone was next considered, and it was shown that the soil, the water and the climate can have little influence in determination of the relative frequency of lithiasis. It was also pointed out that, although the disease as seen in Asia does

not show any indications of change, it has altered remarkably in western Europe during the last fifty or one hundred years. Stone in the bladder in children has become rare, whereas renal lithiasis probably is increasing in frequency. The diminution of formation of stone in childhood was ascribed to better and more hygienic feeding; the cause of the increased frequency of renal lithiasis was stated to be unknown.

The third part of Joly's <sup>51</sup> paper dealt with the preventive treatment of calculous disease. This subject was discussed on general principles. It was emphasized that the incidence of stone in Asia can be greatly diminished by improvement of the social conditions under which the inhabitants live, by enrichment of their diet and by the teaching of the rudiments of hygiene. The disease is thus a problem for the state rather than for the individual physician. It is also possible that the incidence of stone in western Europe may be diminished by measures introduced to improve the general social condition of the people, but Joly expressed the opinion that this is a problem for the future.

In Rydgaard's <sup>52</sup> report in a symposium on stone he stated that the term "primary urinary calculus" is to be understood as meaning "a calculus in a healthy system with sterile urine." He presented a summary of the various theories of the cause of the formation of urinary calculi and of the results up to the time of his writing of experimental formation of calculi; material to illustrate primary urinary calculus was presented. Primary urinary calculi are principally unilateral renal or ureteral calculi. Distribution of them between the right and left sides is 1:1, and between male and female patients, 7:3. Every stone consists of organic and inorganic substance. The inorganic substance is often calcium oxalate, but uric acid, urates and phosphates also occur often. Supersaturation of the urine with crystalloid must occur for the formation of a concretion to take place. On determination of the degree of saturation of the urine, attention must always be paid to the influence of all the urinary electrolytes on each other, by means of which the degree of saturation, which often seems high if this influence is disregarded, is generally considerably reduced. The urinary colloids are of no importance to the solubility of the urinary crystalloids but seem to influence precipitation of such crystalloids and the speed with which it takes place.

Attempts to form calculi experimentally, together with a number of clinical observations, indicate that diet is of extraordinary significance in the formation of primary calculi. In particular, the ingestion of large quantities of ingredients that contain oxalic acid or purine and deficiency of magnesium, calcium and vitamin A (perhaps also of vitamins B, C and D) seem to be able to cause the formation of calculi, which is also

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52. Rydgaard, F.: The Aetiology and Preventive Treatment of Primary Urinary Calculus, *Internat. Soc. Urol., Rep.* (pt. 1) **7**:146-185, 1939.

influenced by various conditions which, acting through changes in metabolism, increase the excretion of oxalate, purine or phosphate. The last is encountered in cases of hyperparathyroidism. Various investigations and facts seem to indicate that something else, not yet ascertained, in addition to supersaturation of the urine (which is an indispensable factor in the formation of every calculus), is necessary. The hypothesis is proposed that this unknown cause may be damage to the kidney itself. Since the cause or source of the hypothetic calculus-forming factor in the kidney itself is not known, the greatest importance in preventive treatment must be attached to prevention of supersaturation of the urine with crystalloids. This prevention is attempted by administration of a sufficiently mixed diet. Food containing oxalic acid and purine must be avoided. The ingestion of liquids must be fairly plentiful, and care must be taken that there is a sufficient content of soluble, absorbable calcium and magnesium salts and also of various vitamins. Prevention of recidivation after treatment for primary urinary calculi is a part of the preventive treatment. This demands careful removal of the original stone or stones and treatment of possible abnormalities within or without the urinary system (for example, parathyroidectomy). Postoperative treatment by means of diet and, if necessary, medicine should then follow, the pH of the urine, its content of crystalloids and so forth, in accordance with the nature of the original stone, being constantly checked.

Randall,<sup>53</sup> in a discussion of the causation of primary renal calculus, stated that in the absence of stasis primary renal calculus is dependent on, and arises because of, a pathologic condition of the renal papillae. This pathologic condition is a varying degree of damage to the structures of the collecting tubules and the supporting interstitial tissue, and this damage is succeeded in living persons by attempted repair, in which process calcium salts may be deposited. Deposition of calcium salts may be both intratubular and extratubular and may occur in varying degrees; in some cases it is slow, discrete and chronic; in others, acute, rapid and overwhelming.

On the basis of Randall's studies at necropsy, two types of calculous disease are distinctly discernible: In type 1 a calcium plaque with a predominance of interstitial deposition occurs, and it evidences a slow, chronic process; in type 2 intratubular deposition occurs, producing the picture of a more drastic process and more rapid accumulation. In calculous disease of type 1 calcium carbonate and calcium phosphate have been identified, and it was suggested that calcium nucleinate may be the remainder. In calculous disease of type 1 the deposition of salt occurs most frequently on the side wall of the papilla, and such deposition

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53. Randall, A.: The Etiology of Primary Renal Calculus, *Internat. Soc. Urol. Rep.* (pt. 1) 7:186-261, 1939.

remains innocent of any part in the causation of stone until growth and pressure (decubitus) bring a plaque of calcium to the surface of the papilla. When such a calcium plaque does become exposed on the surface of the papilla, it is then bathed in calicinal urine and, acting as a foreign body, becomes the nidus on which any urinary salt may crystallize. Calculi of both calcium phosphate and calcium oxalate have been identified as having such origin and growth, and it is to be expected that other salts will be so identified in the future, when technical difficulties have been overcome. On this pathologic basis it can be recognized how a stone gains an opportunity to grow and also how it can remain asymptomatic for long periods. Evidence was presented to show that when a calculus is extruded extrusion is accomplished by tearing from the papilla its foundation of deposit of calcium salts.

In calculous disease of type 2, calcium salts are principally intratubular and may present all gradations, from simple tubular inspissation to drastic choking of tubules and marked tubular damage, with some interstitial deposition in cases in which the condition is advanced.

Randall<sup>53</sup> presented the results of 1,154 studies at necropsy, in which lesions of type 1 were observed in 19 per cent and lesions of type 2 in 1.9 per cent and in which 65 examples of the formation of calculus adherent to the renal papillae were observed.

Randall presented evidence based on hyperparathyroidism in 3 human beings and 32 dogs given parathyroid extract to show that in this condition the initial renal damage is to the epithelium of the tubules and that it precedes the characteristic deposition of calcium salt. Randall<sup>53</sup> concluded that in the course of its normal function the kidney suffers insults from many directions and that the greatest damage therefrom occurs in the convoluted and especially in the collecting tubules of the renal papillae, where the greatest concentration of both normal and abnormal urinary elements occurs. On the basis of these research studies, Randall<sup>53</sup> has been able to prove that primary renal calcification is a reparative response to certain morbid states in the renal papillae, that damage to the epithelial cells lining the renal tubules occurs early and that this damage is the prime essential to the subsequent permanent deposition of calcium salts. Randall<sup>53</sup> suggested that the salt deposited in the form of a calculus will be the salt most ready to crystallize out of solution, whether such crystallization is due to abundance, to disturbed colloidal balance or to the poorly understood laws of crystallization. In Randall's paper there were offered for the first time suggestions as to the common origin of the diversification of chemical constituents of stone, together with an explanation of where, why and how a stone forms, and also an accounting for the static and asymptomatic state during which a stone slowly gains growth.



On the basis of published reports, hyperparathyroidism may be expected to account for not more than 5 per cent of the cases in which clinical primary renal calculus is present. That hypovitaminosis A can be responsible is to be recognized, but in modern civilization it probably can account for but a small portion of the remaining 95 per cent of cases, and it would be generous to credit it with as much as 10 per cent of the cases of primary renal calculus. It was Randall's belief that the products (toxins) of distant focal infection play a major role in the causation of papillary pathologic processes and the causation of stone. The close relation that exists between the so-called calculus age and that during which focal infections occur—25 to 50 years—never has been pointed out, and, although results of clinical studies are too uncertain to be trusted, it was Randall's<sup>53</sup> constant observation that patients who had primary renal calculi consistently had active focal infectious conditions elsewhere. The undoubted fact that toxins other than bacterial (toxins of disease, metabolism or dehydration) may produce a similar renal response must not be forgotten.

The treatment and prevention of primary renal calculus embrace a broad study of the individual patient, an intelligent analysis and control of his urine and the correction of pertinent factors, most of which are distant from the seat of disease.

Harrington<sup>54</sup> reported a clinical study of 480 cases of urinary lithiasis in which the patients were observed in the University of California Hospital. During the first five years calculi were removed from 73 patients, with 2 deaths; nephrectomy was required in 16 cases, with 1 death. The total mortality rate for removal of calculi, regardless of method, from the upper part of the urinary tract was 3.37 per cent. During the last five years calculi were removed from 100 patients, with 4 deaths, and nephrectomy was employed in 34 cases, with 1 death. The total mortality rate was 3.65 per cent. The rate of recurrence has been substantially reduced in the last five years. The increased use of roentgen rays at operation in cases of multiple lithiasis undoubtedly has been a great factor in such reduction. The general rate of recurrence after removal of stones from the kidney by all methods was 18.6 per cent during the first period and 10.9 per cent during the second period.

Flocks<sup>55</sup> stated that in the outlining of a regimen for the prophylaxis and medical management of calcium urolithiasis, the factors of vitamin A deficiency, focal infection, infection of the urinary tract, stasis of the urinary tract, precipitability of urinary calcium and urinary excretion of calcium must all be considered. Flocks<sup>55</sup> discussed the

54. Harrington, H. L.: A Clinical Study of Four Hundred and Eighty Cases of Urinary Lithiasis, *J. Urol.* **41**:507-519 (Oct.) 1940.

55. Flocks, R. H.: Prophylaxis and Medical Management of Calcium Urolithiasis: The Role of the Quantity and Precipitability of the Urinary Calcium, *J. Urol.* **44**:183-190 (Aug.) 1940.

urinary excretion of calcium in the normal person and under pathologic conditions. The relation of such excretion to calcium urolithiasis was emphasized, and a regimen for the management of calcium urolithiasis based on the urinary excretion of calcium was described. The significance of the precipitation of calcium in the urine in relation to calcium urolithiasis was discussed. A method for determination of the quantity of calcium in the patient's urine was described. The results for a small group of normal persons and patients with urinary calculi were given. These emphasized the necessity of following the effects of therapy on the precipitation of calcium in the urine.

*Effect of Alkalis.*—Eisele<sup>56</sup> discussed the role of alkali therapy for peptic ulcer in the formation of urinary calculi. In a series of 505 patients who had kidney or ureteral stones, there were 43, or 8.5 per cent, who suffered from preexisting treated peptic ulcers. There were 13 additional patients, or 2.6 per cent, who had chronic gastrointestinal complaints for which they habitually took alkalis. Thus, there were 56 patients, or 11.1 per cent, for whom the ingestion of alkali powders may have been considered of etiologic importance in the formation of their urinary stones. This is in agreement with theoretic considerations and constitutes the clinical counterpart of experimental production of stones in laboratory animals by the feeding of crystalloids. Eisele<sup>56</sup> expressed the opinion that the hyperexcretory calculus which developed among these patients demonstrates the potential danger of alkali therapy for peptic ulcer.

Turell<sup>57</sup> stated that urolithiasis may be produced by extrarenal foci of infection or on the basis of preexisting infection of the urinary tract. Urinary infection caused by organisms of the colon bacillus group may be an important factor in the genesis of urolithiasis. Inflammatory and suppurative lesions of the anorectocolonic tube and dysfunction (stasis of fecal current) were considered to be important foci of infection. The colon also may act as a portal of entry for enteric organisms into the blood and lymph streams. Eradication of these lesions and correction of dysfunction are important parts of the therapeutic program for the elimination and prevention of urolithiasis with infection caused by the organisms of the colon bacillus group.

#### CYSTINURIA

Hammer and Thompson<sup>58</sup> reviewed the literature and reported on the patients suffering from cystine lithiasis encountered at the Mayo

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56. Eisele, C. W.: Role of Alkali Therapy for Peptic Ulcer in Formation of Urinary Calculi, *J. A. M. A.* **114**:2363-2366 (June 15) 1940.

57. Turell, R.: The Intestinal Phase in Urologic Disease: III. The Rôle of the Colon in Urolithiasis, *J. Urol.* **43**:476-480 (March) 1940.

58. Hammer, H. J., and Thompson, G. J.: Cystine Lithiasis: A Clinical Study. *Urol. & Cutan. Rev.* **44**:341-355 (June) 1940.

Clinic during the years 1930 to 1938 inclusive. During this period 16 instances of cystine lithiasis and 5 instances of cystinuria without lithiasis were recognized. It seems likely, Hammer and Thompson<sup>58</sup> wrote, that many instances of cystinuria were not detected. The authors stressed the importance of obtaining a familial history when the diagnosis of cystine lithiasis is to be made. The test used to determine the presence of cystine in the urine is Osterberg's modification of the Sullivan test. It is performed as follows: To 5 cc. of urine add about 0.3 cc. of a 50 per cent solution of hydrochloric acid (or add the acid until the urine reacts acidly to congo red paper). Then add 2 cc. of fresh 5 per cent solution of sodium cyanide. Mix and let reduction proceed for ten minutes at room temperature; then add 1 cc. of fresh 0.5 per cent solution of 1, 2-naphthoquinone-4-sodium sulfonate. Mix and add 5 cc. of 10 to 20 per cent solution of anhydrous sodium sulfite in 0.5 normal sodium hydroxide. Mix and let stand for thirty minutes. Add 1 cc. of a 2 per cent solution of sodium hyposulfite in 0.5 normal sodium hydroxide. If a red color forms, cystine is present. Usually, seven standards are prepared in a similar manner for quantitative determinations.

Hammer and Thompson<sup>58</sup> advocated employment of a low cystine diet and alkalinization of the urine in the treatment of cystine lithiasis. They also recommended surgical removal of the calculi. Of the 16 patients studied, 12 were males. The average age at which onset occurred was 16.4 years. Pain was the most common symptom. A history of the passage of gravel was obtained from 13 of the 16 patients. Twelve patients had or had had bilateral calculi. In each case a positive response to the test for cystinuria was obtained. The calculi cast opaque shadows in the original roentgenogram of the urinary tract in 12 of the 16 cases. In the 4 other cases calculi had been passed by the patients at some previous period, and the urine contained cystine. Retrograde or excretory urographic study did not reveal any evidence of lithiasis in these instances. Alkalis and diets (low protein, low cystine and alkaline ash) were advised for all patients. Postoperatively, immediate alkalinization seems advisable to prevent early recurrence.

#### BACILLURIA (MYCO. TUBERCULOSIS)

Rosencrantz<sup>59</sup> made a urologic study in 200 cases in which proved chronic pulmonary tuberculosis had afflicted men. The genital tract was examined, and guinea pigs were inoculated with urine.

Tuberculosis of the epididymis was found 41 times and tuberculosis of the seminal vesicles 5 times, always in conjunction with tuberculosis

59. Rosencrantz, E.: Frequency of Tubercle Bacillus in Urine of Chronic Pulmonary Tuberculosis in Relation to Urogenital Complications, *J. Urol.* **44**:498-506 (Oct.) 1940.

of the epididymis. Tuberculosis of the prostate gland was not found clinically; in 1 case it was observed microscopically after necropsy. McKenna and Sweany found this condition in 4.2 per cent of their cases of advanced pulmonary tuberculosis. According to the views of Thomas and Kinsella, the kidney is first infected, and this causes Myco. tuberculosis to appear in the urine; the prostate gland is then involved; there, in turn (via the prostatic ducts) the seminal vesicles are infected, and then the epididymis is infected, despite the fact that clinically only the epididymis seems involved. Tuberculosis of the kidney combined with tuberculosis of the epididymis was found in only 1 of 41 cases studied. Mombaerts and Laroche were said to have found combined renal and genital lesions in 31 per cent of their 184 cases of renal tuberculosis. Hobbs, in 1,000 cases of pulmonary tuberculosis in which study was carried out at necropsy, observed renal lesions in 16.2 per cent. The low incidence in Rosencrantz's<sup>59</sup> paper may be explained by the fact that the study was essentially a clinical one; studies carried out at necropsy doubtless would have increased the percentage of renal involvement.

#### INFECTIONS OF THE URINARY TRACT

Austen<sup>60</sup> stated that since in cases of infection of the urinary tract sulfanilamide directly exerts the effect of an antiseptic agent on the organism, direct instillation of the drug into the renal pelvis should be of value in certain cases, particularly those in which the patient tolerates the drug poorly when it is administered by the usual routes; those in which renal function is reduced; those in which there is an anatomic or pathologic abnormality which prevents high local concentration of the drug, and those in which there is interference with renal drainage. Austen<sup>60</sup> presented the results of treatment of 10 patients who had infection of the upper part of the urinary tract. Direct instillation of a sulfanilamide compound (sulfanilamide with maltose) into the renal pelvis was done. When the drug was administered in this manner, it was well tolerated in all except 1 case. A definite clinical and bacteriologic improvement was noted in 8 cases, a bacteriologic cure was obtained in 1 case, and no improvement resulted in 1 case. Observations on the concentration of sulfanilamide in the blood, in urine obtained from the treated kidney and in urine obtained from the untreated kidney, demonstrate that the drug is absorbed from the renal pelvis into the blood stream in appreciable amounts and that it is also excreted in the urine from the kidney into which no injection was made. The concentration of sulfanilamide in urine from the kidney into which the drug was injected reaches a much higher value than is possible when the drug is

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60. Austen, G., Jr.: Pelvic Lavage with Sulfanilamide in the Treatment of Renal Infections, *J. Urol.* **43**:637-653 (May) 1940.

administered by the oral or the subcutaneous route. As a result of these observations, Austen<sup>60</sup> said that although it is a method of administration which has definite limitations, direct pelvic instillation of sulfanilamide is a worth while procedure in selected cases of renal infection.

The type of infection present and therefore the mode of treatment to be instituted may be determined readily in cases of infection of the urinary tract by use of a simple type of Gram's stain. This stain demonstrates the type of organism present (coccus or bacillus) and its reaction (positive or negative). Cook and Sutton<sup>61</sup> stated that the majority of infections of the urinary tract are caused by gram-negative bacilli (*E. coli* [predominantly]; *Aerobacter aerogenes*; *Pseudomonas*; *Salmonella*; *Proteus*; *Shigella*; *Alcaligenes*). Further differentiation of these may be done on eosin-methylene blue agar plates. All yield to the same therapeutic attack (acidification with mandelic acid and similar agents) except *Proteus*, a urea-splitting organism which causes a high urinary  $p_H$ . Cocci cause 20 per cent of all urinary infections, which, excepting those caused by the gonococcus, are caused by gram-positive organisms. A simple stain will distinguish *Streptococcus faecalis* from all other streptococci and all streptococci from staphylococci and micrococci. Special mediums are necessary for growing the cocci. Pathologic changes depend on (1) virulence of the organism, (2) degree of infection and (3) resistance of the patient. However, the type of organism present is to a certain extent a factor. *E. coli*, *A. aerogenes* and *Proteus* produce progressively deeper and more ineradicable lesions. Therapy with mandelic acid will cure all these infections, including those due to forms of the *Proteus* genus when such forms do not have the power to split urea. Eradication of both coincidental pathologic deformity, whether primary or secondary to the infection, and focal infection is important, particularly in the prevention of urinary stagnation. It is doubtful whether *Pseudomonas* is ever a primary invader. *Str. faecalis*, the most common form of coccus in relation to urinary infection, is, when it is found in this particular type of infection, almost invariably secondary to nephrostomy or manipulation. Micrococci clinically may be pathogenic, and eradication of them may result in complete symptomatic relief. Cocci characteristically produce greater deformity of the ureters than of the pelvis; the converse is true of bacilli. Mandelic acid causes fewer untoward reactions than does sulfanilamide, but the latter is better for attack on urea-splitting organisms or for therapy in cases of impaired renal function, even when bacilli are the causative organisms. *Str. faecalis* responds better to mandelic acid therapy, but other coccic infections should be treated with sulfanilamide or neoarsphenamine (administered intravenously) plus acidification. Treat-

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61. Cook, E. N., and Sutton, E. B.: Infections of Urinary Tract, with Particular Reference to Causative Organism, *J. Urol.* **42**:880-885 (Nov.) 1939.

ment of associated pathologic conditions is very important; release of urinary stagnation is especially important. Against the gonococcus, which has its own characteristics on smear and culture, sulfapyridine is the drug of choice.

#### GONORRHEA

*Arthritis.*—Culp<sup>62</sup> studied a series of 200 cases of gonorrheal arthritis in an effort to determine the most satisfactory form of therapy. His cases included 105 in which the condition was acute, 50 in which it was subacute and 45 in which it was chronic. Of the forms of treatment employed, those in which sulfanilamide, mercurochrome (the disodium salt of 2,7-dibromogammahydroxymercurifluorescein) administered intravenously and fever therapy were used gave the best results. Sixty-nine per cent of the 29 patients treated intravenously with mercurochrome were discharged well or markedly improved. Excellent results were obtained with patients who had chronic and subacute conditions, as well as with those who had acute conditions. The dose varied from 10 to 30 cc. No serious reactions were encountered. Generally only three or four doses were required. When the initial doses were small, the number required was usually greater. Only 53 per cent of the 19 patients who received fever therapy became well or markedly improved. Several patients had severe reactions, and 1 died while undergoing treatment. Cures were effected in the chronic as well as the earlier stages. This treatment, Culp wrote, is strictly a procedure to be used in hospitals and has definite contraindications. Twenty-two patients were treated with sulfanilamide, and 68 per cent of these left the hospital well or markedly improved. In most of the cases the condition was acute, and the patients showed amazing improvement, despite osseous changes in a few instances. The total dose varied from 14.4 to 105.6 Gm., and the duration of therapy varied from three to twenty-two days. Values for the content of the drug in the blood of the patients were followed in most cases and varied from 2.8 to 20 mg. per hundred cubic centimeters. Most of the patients had mild toxic symptoms; anemia developed in 6; 1 required a transfusion of blood, and in another marked leukopenia developed. No fatalities resulted.

Chemotherapy appeared to be more efficacious than any of the other forms of treatment. Sulfanilamide and mercurochrome (administered intravenously) were recommended by Culp<sup>62</sup> for the routine treatment of gonorrheal arthritis, and each seemed to him to be of about the same therapeutic value. Both often produced surprisingly rapid cures. Fever therapy was of marked benefit in some cases, but reactions to it were more severe than to other forms of treatment. It was not condemned

62. Culp, O. S.: Treatment of Gonorrheal Arthritis: An Analysis of Two Hundred Cases, *J. Urol.* **43**:737-765 (May) 1940.

on the basis of the small group of cases reported by Culp, but it was said to involve more risk than other forms of treatment and also was said to be much more heroic than the chemical methods. The initial dose of mercurochrome should be 15 cc. of a 1 per cent solution, followed by 17, 19 and 21 cc. after intervals of three or four days or longer, according to the reactions produced. A sharp increase in temperature may be considered the equivalent of the production of antibodies or of a defense reaction and is of therapeutic value. Sulfanilamide should be administered in doses sufficient to maintain a content of the drug in the blood of 8 mg. per hundred cubic centimeters if possible. This can be accomplished most readily by administration of 1.2 Gm. (about 20 grains) with an equal amount of sodium bicarbonate every six hours until the desired concentration in the blood has been reached. The subsequent maintenance dose of the drug may be increased or reduced according to the indications provided by the content of the drug in the blood and the therapeutic effect on the arthritis. Sulfanilamide rarely should be administered for longer than two weeks, and careful chemical studies of the blood should be made at frequent intervals (daily, if possible) during treatment.

Roth<sup>63</sup> stated that in 47 per cent of 44 cases of acute gonorrhea in which patients were treated with sulfanilamide cure resulted in two weeks or less and that in 22 cases of acute gonorrhea in which patients were treated with sulfanilylsulfanilamide (paraaminobenzenesulfonyl-paraaminobenzenesulfonamide) cure resulted in 73 per cent. In 42 cases of acute gonorrhea in which private patients were treated with sulfanilamide plus irrigation with acriflavine hydrochloride and potassium permanganate, 71 per cent of the patients were cured within two weeks or less; in 29 cases of acute gonorrhea in which private patients were treated with sulfanilylsulfanilamide plus daily irrigation with acriflavine hydrochloride and potassium permanganate, 92 per cent of the patients were cured within two weeks or less.

Twelve patients who did not respond to therapy with sulfanilamide were cured when sulfanilylsulfanilamide was employed. The dose of sulfanilamide never was more than 45 grains (3 Gm.) a day. The routine dosage of sulfanilylsulfanilamide was 45 grains (3 Gm.) in the outpatient department of the department of urology of Ohio State University at Columbus, Ohio, and in the treatment of private patients it was 45 grains (3 Gm.) the first two days and 30 grains (2 Gm.) daily thereafter. Neither drug was administered for more than two weeks. Roth<sup>63</sup> stated that his experience has proved that sulfanilyl-

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63. Roth, L. J.: Sulfanilyl-Sulfanilamide (Disulon) Versus Sulfanilamide in the Treatment of Acute Gonorrhea in the Male, *J. Urol.* **43**:483-490 (March) 1940.

sulfanilamide is superior to sulfanilylsulfanilamide in attacks on the gonococcus. When response to either sulfanilamide or sulfanilylsulfanilamide is not immediate, clinical cure is prolonged by from four to six weeks, and it may be wise, Roth suggested, to discontinue chemotherapy and to employ other methods of treatment to prevent the occurrence of unnecessary toxic effects referable to prolonged administration of whichever drug is used. Reactions produced by sulfanilylsulfanilamide (noticed in 25 per cent of cases) were much less than those produced by sulfanilamide (noticed in 60 per cent of cases). The complication of peripheral neuritis was observed in only 1 of the 63 cases in which patients were treated with sulfanilylsulfanilamide.

#### SULFANILAMIDE AND DERIVATIVES

*Sulfanilamide.*—Sickler<sup>64</sup> stated that after the oral administration of sulfanilamide the drug is excreted by the kidney in a quantity sufficient to render the urine bactericidal for most organisms commonly found in the presence of infections of the urinary tract. At a given  $p_H$ , the intensity of the bactericidal effect appears to be directly proportional to the concentration of the drug in the urine. The reaction of the urine is a factor of major importance. When the same concentration of sulfanilamide was maintained constantly, more favorable bactericidal results were demonstrated in alkaline urine at  $p_H$  7.7. Bacteriostatic or bactericidal effects were observed in 79 per cent of tests on forty-three strains of organisms in specimens of urine of  $p_H$  7.7 containing 80 mg. of the drug per hundred cubic centimeters. Different strains of the various organisms tested were not equally susceptible to the same concentration of sulfanilamide in the urine. Nine of the forty-three strains mentioned were resistant to the bactericidal effect of 80 mg. of sulfanilamide in 100 cc. of urine at  $p_H$  7.7. Increase of the concentration to 200 mg. per hundred cubic centimeters (an increase of more than 100 per cent) affected only three of the nine resistant organisms. In view of the known toxic manifestations which this drug causes, the maintenance of such high urinary concentrations of sulfanilamide, in the opinion of Sickler,<sup>64</sup> is only rarely justifiable.

Growth of bacteria was not inhibited in urine which had a  $p_H$  of less than 9.5. At this level members of the colon, aerogenes, Salmonella and Pseudomonas groups were killed. Staphylococcus aureus and Proteus vulgaris were not affected by this degree of alkalinity. Since the maximal alkaline titer in urine from human beings never approaches such a figure, alkalinity alone has no bactericidal value in the treatment of infections of the urinary tract.

64. Sickler, J. R.: A Study of the Bactericidal Activity of Sulfanilamide in Urine at Various Levels of Hydrogen Ion Concentration, J. Urol. 43:906-916 (June) 1940.



*Sulfathiazole*.—Culp<sup>65</sup> reported results obtained in the treatment with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) of 30 patients who, among them, had a great variety of infections of the urinary tract. In 24 cases an attempt was made to sterilize the urine completely. The result in 16 (66.7 per cent) was elimination of all infection. Three patients were unable to tolerate sulfathiazole and were considered to have been inadequately treated. One complete failure was noted. Organisms which were killed by sulfathiazole in this series of cases were *Staphylococcus albus*, *Staph. aureus*, *Proteus vulgaris*, *coli*, *A. aerogenes*, *Corynebacterium xerosis* and *Streptococcus mitis alpha*. The most resistant organism was *Str. faecalis gamma*. Sulfathiazole was administered to 6 additional patients only while they had acute pyelitis. Symptomatic improvement followed quickly in each case. No attempts were made to sterilize the urine of these patients, because all patients had indwelling catheters. Of the entire group of 30 patients who received sulfathiazole, toxic manifestations were experienced by 23.3 per cent. No serious end results were noted. All toxic symptoms disappeared on withdrawal of the drug. Most patients received 1 Gm. of sulfathiazole every six hours for five to ten days. The content of the drug in the blood was highest in those patients who experienced toxic symptoms, but it was less than 1 mg. per hundred cubic centimeters in the blood of several patients who were cured. The content of the drug in the urine is a more accurate index of the progress of treatment, Culp<sup>65</sup> stated, than is the content of the drug in the blood.

Sulfathiazole appears to be an excellent urinary antiseptic agent if it is administered under favorable conditions and with great care. The toxic symptoms which it causes makes it imperative for the physician to follow all patients at frequent intervals. Routine hospitalization should be employed if possible. Restriction of the intake of fluid should be avoided if possible.

*Urologic Complications of the Use of Sulfanilamide Compounds*.—Carroll, Shea and Pike<sup>66</sup> stated that supersaturation of acetylsulfapyridine crystals during the administration of sulfapyridine is sufficient at times to cause complete obstruction in the urinary tract. This condition can be relieved promptly and satisfactorily by the cystoscopic insertion of catheters in the ureters and pelves and by lavage with warm physiologic solution of sodium chloride or sterile water. These crystals, which cause obstruction, are not opaque to roentgen rays even in large amounts;

65. Culp, O. S.: Sulfathiazole Treatment of Urinary Tract Infections. *J. Urol.* **44**:116-124 (July) 1940.

66. Carroll, G.; Shea, J., and Pike, G.: Complete Anuria Due to Crystalline Concretions Following the Use of Sulfapyridine in Pneumonia. *J. A. M. A.* **114**: 411-412 (Feb. 3) 1940.

therefore a flat roentgenogram is of no value. Symptoms of renal colic and/or hematuria should make the physician suspicious of crystalline concretions in the urinary tract and should not be mistaken for symptoms of gastric disturbance. Hematuria noted clinically probably is the result of minute traumatization of the mucous membranes by the crystals rather than the result of damage to the renal parenchyma and therefore is of no grave consequence. The forcing of fluids in conjunction with sulfapyridine therapy probably is appropriate, since it will relieve, to some extent, supersaturation of the urine. It was incidentally suggested that supersaturation of any form of crystals in the urine may result in calculous formation. Death of Carroll, Shea and Pike's<sup>66</sup> patient was prevented apparently by cystoscopic manipulation, and the fact that the patient's life was saved warranted this prompt report.

Antopol<sup>67</sup> stated that hematuria which was only microscopically detectable was encountered in 16 of 40 cases in which patients were treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). In 1 case in which necropsy was performed, calculi were not demonstrable in the urinary tract, although hemorrhagic papillitis and pyelitis had been present. Typical ureteral colic, accompanied with hematuria which disappeared promptly after discontinuance of administration of sulfapyridine, was observed. In 1 case anuria occurred two days after sulfapyridine therapy had been instituted. Residual symptoms were not present in any of the cases at the time of discharge of the patients from the hospital.

Plummer and McLellan<sup>68</sup> reported on 2 patients in whom renal calculi developed after sulfapyridine treatment. Existence of calculi was proved in 1 case at postmortem examination and in the other by pyelographic study. The patients in both had hematuria, and 1 also had renal colic. One had received only 11 Gm. of the drug and the other 555 Gm. Pyelograms in 1 of the 2 cases demonstrated calculi which were nonopaque to roentgen rays. The serial study indicated that later the calculi had dissolved or had been washed out and renal function had returned to normal. The features of these 2 cases, together with the experimental studies reported by other investigators, indicate that hematuria and other urinary symptoms occurring after the administration of sulfapyridine are caused by the deposition of sulfapyridine crystals and concretions in the kidneys and ureters. Frequent examination of the urine, particularly for erythrocytes, should be made during therapy with sulfapyridine. Administration of the drug should not

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67. Antopol, W.: The Occurrence of Urologic Complications in Humans Following Sulfapyridine Therapy, *J. Urol.* **43**:589-597 (April) 1940.

68. Plummer, N., and McLellan, F.: The Production of Sulfapyridine Renal Calculi in Man Following Administration of Sulfapyridine, *J. A. M. A.* **114**:943-946 (March 16) 1940.

be initiated or should be done very cautiously if hematuria occurs or if the patient is known to have diminished renal function.

Stryker<sup>69</sup> discussed the nature of the renal lesion which sometimes occurs when therapy with sulfapyridine is employed. He reported a case in which a child 5 years old died of persistent pneumococcic meningitis. At necrosy the kidneys were greatly enlarged, weighing 85 Gm. each, as compared with a normal average weight of 25 Gm. for a patient of that age. The cut edges bulged markedly. In the calices and pelves of both kidneys was a small amount of yellow-white gravel; from the pelvis of the right kidney four calculi measuring as much as 1.5 mm. in diameter were isolated. Neither the pelvis nor the ureter was dilated. In both ureters and in the bladder there was gravel similar to that found in the kidneys; this gravel was most prominent at the entrance of the ureters into the bladder. The mucosa of the urinary tract appeared to be normal. Precipitation of acetylsulfapyridine in the kidney was observed. Stryker<sup>69</sup> stated that marked dilatation of the cortical tubules and glomerular spaces characteristic of the kidneys in instances of toxicity caused by sulfapyridine seems to depend on intratubular precipitation of the drug or its compounds.

#### URINARY SECRETION IN THE CHICKEN

Hester, Essex and Mann<sup>70</sup> discussed the results obtained by previous investigators and pointed out that either the figures on renal urinary output are much too high or there must be a selective resorption of water by the cloacal mucosa. They used three methods of study. First, they found that ureteral cannulization performed with local anesthesia demonstrated diuresis immediately after the operation. Figures comparable to those obtained by previous workers were obtained. Subsequently, much lower figures (2.5 cc. per half hour; 120 cc. per day) were obtained. Caffeine and dextrose were employed as diuretic agents. Solution of posterior pituitary decreased the urinary flow in 1 experiment. Second, collection of the urine was done by obstruction of the rectum when necessary and by the placing of a small funnel in the urodeum. High outputs of urine were obtained by this method as well as when the birds were disturbed. Outputs of urine were much lower when determinations were made repeatedly and when the birds were undisturbed. The third method as described by Hester, Essex and Mann<sup>70</sup> for collection of avian urine from exteriorized ureteral orifices is a new one. By this method much smaller amounts were obtained consistently than was possible by the other methods. The amounts

69. Stryker, W. A.: The Nature of the Renal Lesion with Sulfapyridine Therapy, *J. A. M. A.* **114**:953-954 (March 16) 1940.

70. Hester, H. R.; Essex, H. E., and Mann, F. C.: Secretion of Urine in the Chicken (*Gallus Domesticus*), *Am. J. Physiol.* **128**:592-602 (Feb.) 1940.

varied from 61 to 123.5 cc. in eighteen collections. The urine was thick, tenacious and mucoid and contained an abundance of urates. The oral intake of water of the birds studied was from 50 to 250 cc. daily.

The observations of Hester, Essex and Mann<sup>70</sup> support the belief that elimination of urine in birds is fundamentally the same as the process in mammals and that the cloaca has the same function (as a receptacle) as has the urinary bladder in mammals. Diuresis can be produced by relatively minor disturbances of the bird.

#### UROGRAPHY

Braasch and Doss<sup>71</sup> stated that the difficulty of determination of the cause of stasis as visualized in the delayed urogram often diminishes the clinical value of such a urogram. It is possible that more precise methods of determining ureteropelvic physiologic conditions may aid in this respect. However, the delayed urogram often is of definite value in determination of ureteropelvic obstruction, particularly in cases in which the condition is said to be "borderline." Unless the existence of stasis can be visualized in such cases, surgical intervention usually is not indicated. The delayed urogram also may be of value in identification of doubtful roentgen shadows in the ureter or kidneys.

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71. Braasch, W. F., and Doss, A. K.: The Clinical Value of the Delayed Urogram, *J. Urol.* **43**:617-622 (April) 1940.

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## CHANGES IN THE LIVER ASSOCIATED WITH HYPERTHYROIDISM

WITH A STUDY OF PLASMA PROTHROMBIN LEVELS IN THE  
IMMEDIATE POSTOPERATIVE PERIOD

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During the past nine years considerable interest has been aroused concerning the state of the liver in patients with hyperthyroidism, and excellent studies of the morphologic and physiologic changes in this organ associated with increased activity of the thyroid gland have been reported. Despite the evidence of such a possible relation, however, many patients with hyperthyroidism are treated without regard for hepatic function so far as the type of diet is concerned. Attention has been focused on a high caloric intake, with disregard of the carbohydrate-fat ratio and the vitamin requirements.

### ANATOMIC CHANGES

Cameron and Karunaratne<sup>1</sup> have summarized the development of knowledge concerning the hepatic changes accompanying hyperthyroidism, and Boyce and McFetridge<sup>2</sup> have reviewed the significant clinical and pathologic contributions which have been made to this subject in recent years.

In 1932, Weller,<sup>3</sup> in studying the morphologic changes in the livers of 48 patients who died with hyperthyroidism, compared the data with those on a group of controls who were carefully selected to rule out

This study was carried out under a grant from the John and Mary R. Markle Foundation.

From the Department of Surgery of the New York Hospital and Cornell University Medical College.

1. Cameron, G. R., and Karunaratne, W. A. E.: Liver Changes in Exophthalmic Goiter, *J. Path. & Bact.* **41**:267 (Sept.) 1935.

2. Boyce, F. F., and McFetridge, E. M.: Studies of Hepatic Function by the Quick Hippuric Test: II. Thyroid Disease, *Arch. Surg.* **37**:427 (Sept.) 1938.

3. Weller, C. V.: Hepatic Pathology in Exophthalmic Goiter, *Ann. Int. Med.* **7**:543 (Nov.) 1933.

diseases known to cause pathologic changes in this organ. He found that chronic patchy parenchymatous interlobular hepatitis was the characteristic lesion and noted it to be present to a marked degree in 26 of the 48 subjects and to be slight in 16. In only 6 were no hepatic lesions present. In contrast, in the control series of 48, only 1 liver showed marked interlobular hepatitis; 14 presented slight changes, and 33 were normal.

Beaver and Pemberton<sup>4</sup> in the same year studied 107 autopsies on patients with hyperthyroidism and described in detail three types of pathologic changes in the liver in these cases. These were represented (1) by acute degenerative hepatic lesions varying from fatty degeneration to acute parenchymatous necrosis, the distribution of which was in some instances central and in others focal; (2) by chronic atrophy in which reduction in the weight of the liver with diminution in the size of the hepatic cells were the chief observations, and (3) by chronic cirrhosis similar to the change described by Weller. Beaver and Pemberton were able to correlate the acute degenerative hepatic lesions with those present in cases of severe clinical hyperthyroidism and found that in 57 per cent of the entire series hepatic necrosis was a feature. In all but 2 patients with a basal metabolic rate above +60 per cent acute hepatic lesions were present. They noted further that the acute changes were usually found in patients whose hyperthyroidism was of short duration. Finally, all patients who died in crisis showed acute degenerative lesions in the liver. Chronic cirrhotic changes and simple atrophy were found in the livers of patients with long-standing hyperthyroidism and patients in the older age group. In their series of 107 cases, jaundice was a significant feature clinically in 21.5 per cent and could be explained on the basis of the hepatic lesion in all but 4 cases.

Shaffer<sup>5</sup> has recently reviewed the subject, adding a carefully studied series of 24 autopsies on patients with hyperthyroidism, and has confirmed the findings of Weller and of Beaver and Pemberton. He added that the changes in the liver apparently are not due to deficiencies of vitamins B and C.

In the surgical service of the New York Hospital 680 patients with hyperthyroidism have been subjected to some form of operation on the thyroid gland in the past eight years, and 16 of these have died. Of this group of 16, 8 died in typical thyroid crisis. Autopsies were performed on 6 of the 16. The pathologic changes in the liver in this group of 6 patients resembled those described by Beaver and Pemberton.

4. Beaver, D. C., and Pemberton, J. deJ.: *Pathological Anatomy of Liver in Exophthalmic Goiter*, *Ann. Int. Med.* 7:687 (Dec.) 1933.

5. Shaffer, J. M.: *Disease of the Liver in Hyperthyroidism*, *Arch. Path.* 29:20 (Jan.) 1940.

In the accompanying table are listed the significant clinical and pathologic data in the 6 cases. The weight of each liver was within normal limits. Grossly, the picture varied from that of a liver of normal color and consistency to that of finely nodular cirrhosis with increased consistency. All of the livers exhibited moderate to marked amounts of yellow mottling. Microscopically, the three outstanding observations were (1) large droplets of fat diffusely distributed in the parenchymatous cells; (2) central necrosis of the hepatic cords as evidenced by karyolytic and pyknotic nuclei, eosinophilic, homogeneous cytoplasm and actual loss of cells, with marked infiltration of the necrotic areas by polymorphonuclear leukocytes and red blood cells, and (3) a moderate to marked degree of connective tissue proliferation in the portal spaces, with accumulation of lymphocytes. In case 5 there was a typical picture of moderate nodular cirrhosis.

*Changes in the Liver in Cases of Fatal Hyperthyroidism*

Case	Jaundice	Weight, Gm.	Atrophy	Gross and Microscopic Condition of Liver		
				Fatty Degeneration	Focal or Central Necrosis	Chronic Cirrhosis
1	0	1,700	0	++	0	0
2	0	1,650	0	++	++	0
3	0	1,745	0	++	+++	++
4	+	850	0	+++	++++	++
5	++	1,450	0	+++	0	+++
6	0	1,600	+	++	0	0

+, slight; ++, slight to moderate; +++, moderate to severe; +++, severe.

#### REPORT OF CASES

CASE 1.—The patient was a 54 year old white man with a large, mildly toxic nodular goiter. He was operated on, under avertin with amylene hydrate and nitrogen monoxide and oxygen anesthesia, and showed no marked postoperative reaction. He died one month later of bronchopneumonia, and at autopsy the liver showed only a moderate degree of fatty degeneration.

CASE 2.—A 35 year old white woman was admitted to the hospital with a toxic diffuse goiter and cardiac damage secondary to the hyperthyroidism. Her symptoms were of one year's duration, and on admission her basal metabolic rate was + 65 per cent. After an adequate preoperative preparation of four weeks' duration she was subjected to a subtotal thyroidectomy, under avertin with amylene hydrate and ether anesthesia. At the time of closure of the incision and without previous untoward reaction the patient's heart suddenly ceased beating, while respirations continued for several seconds. Attempts at resuscitation were of no avail. Clinically, the impression was that ventricular fibrillation was the cause of death. At autopsy the heart was essentially normal grossly and showed only small areas of subepicardial fragmentation of the myocardial fibers microscopically. The liver exhibited a moderate degree of fatty degeneration and acute focal necrosis.

CASE 3.—A 45 year old white woman had a toxic nodular goiter and severe congestive heart failure of two years' duration, secondary to chronic endocarditis



Fig. 1.—Photomicrograph of the liver in case 4, showing advanced necrosis in the central three fourths of each lobule.  $\times 90$ .



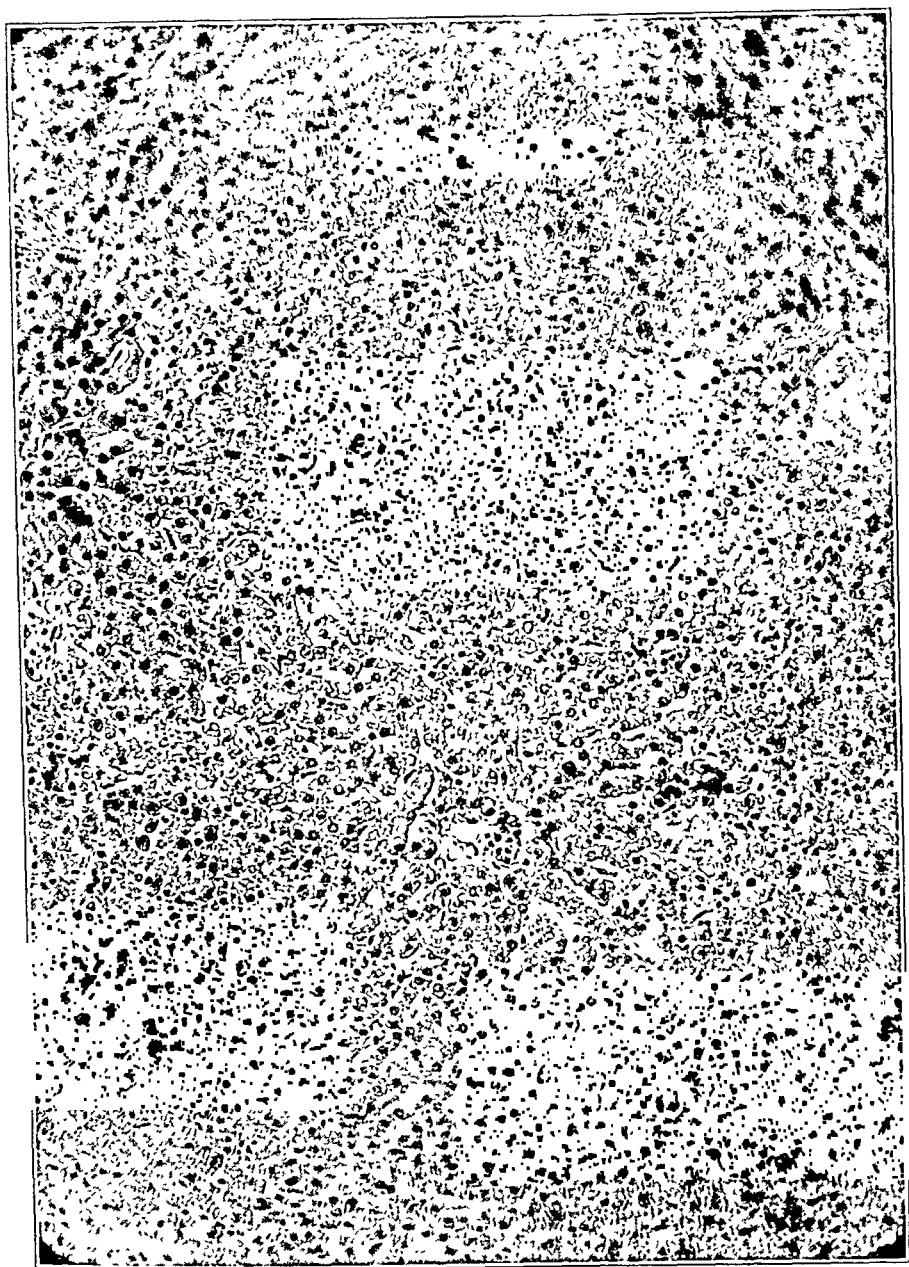


Fig. 2.—Higher magnification of figure 1, showing a portal space with vacuolations of the periportal cells and necrosis of the surrounding cells with polymorphonuclear leukocytic infiltration.  $\times 270$ .

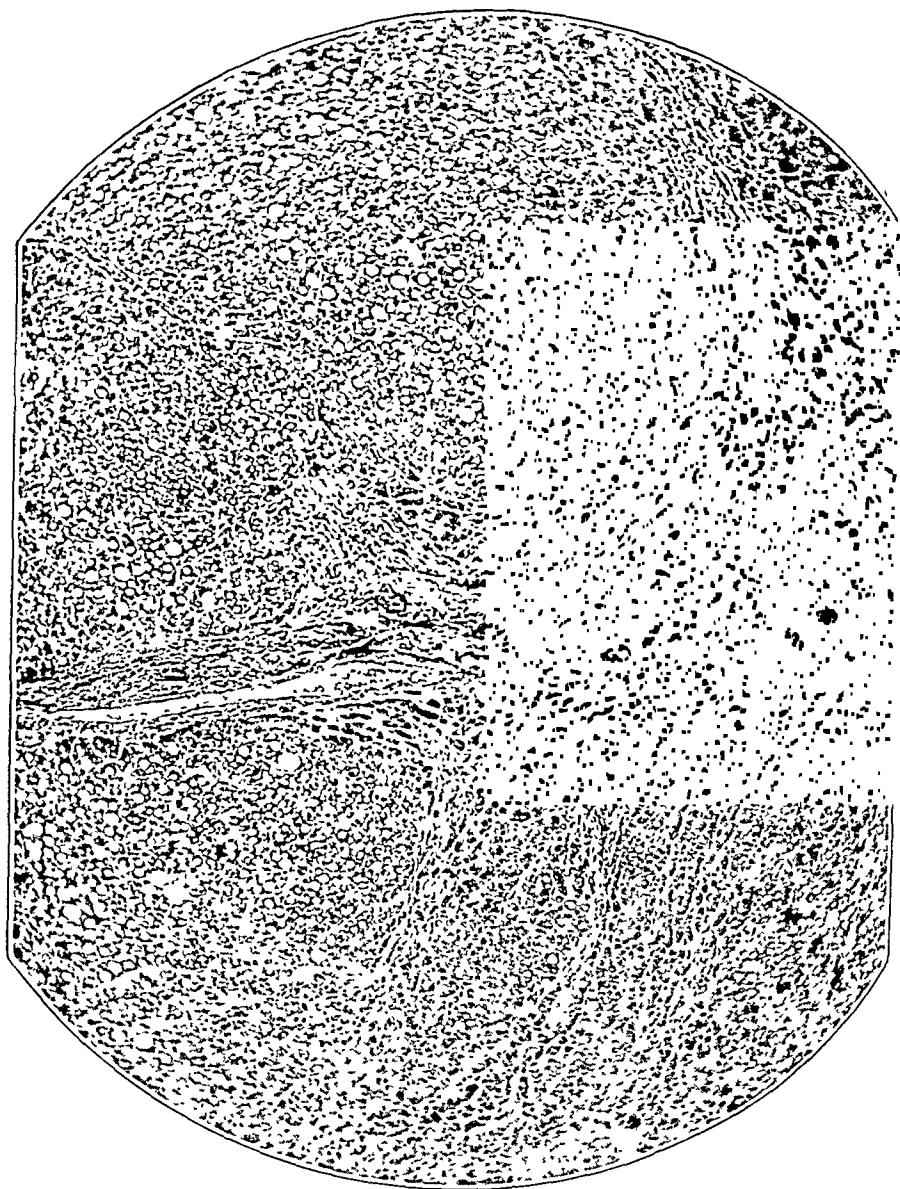


Fig. 3.—Photomicrograph of the liver in case 5, showing advanced fibrosis of a portal space and vacuolation of the central cells.  $\times 90$ .

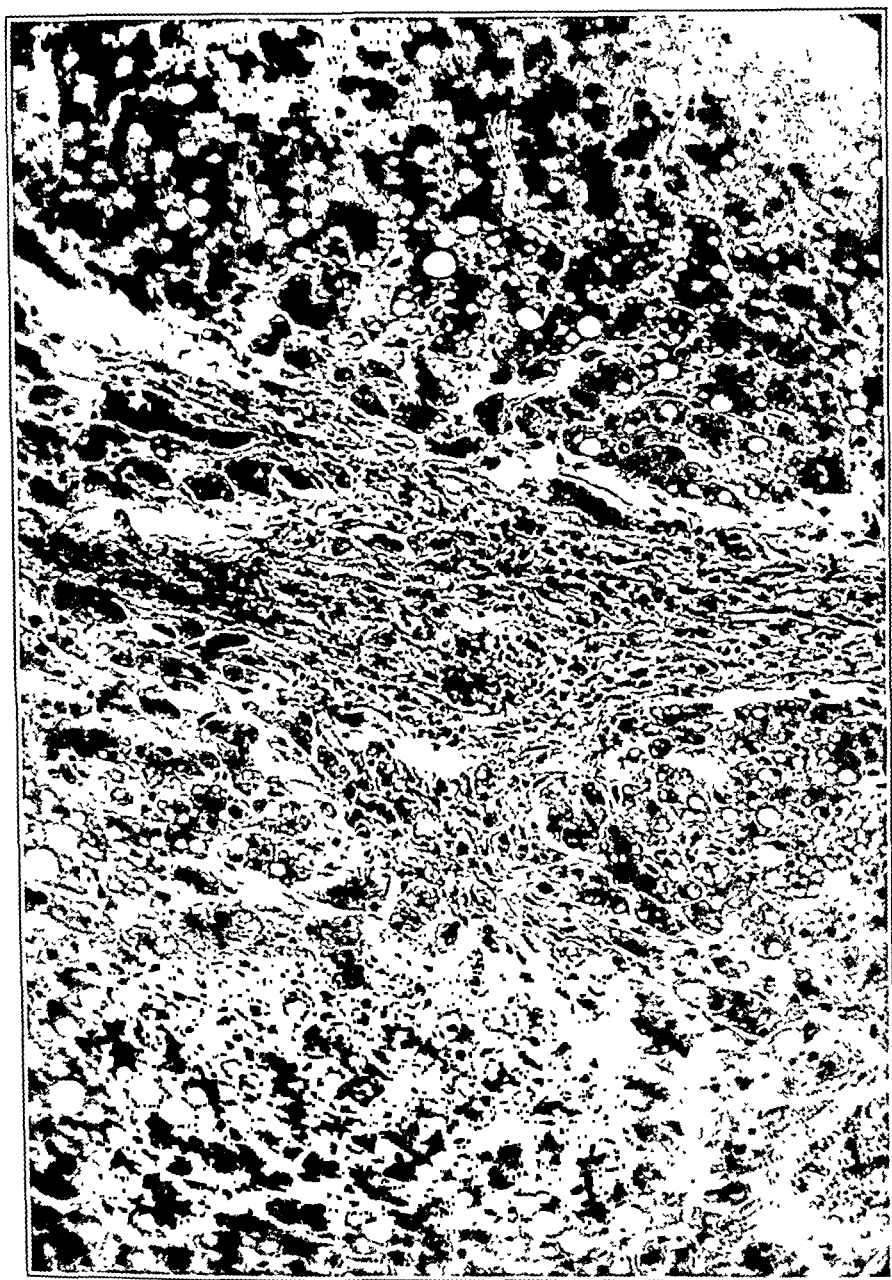


Fig. 4.—Higher magnification of figure 3, demonstrating proliferation of connective tissue and infiltration by round cells.  $\times 270$ .

with mitral stenosis. After several months of preparation, the patient was subjected to a hemithyroidectomy, with the region under local anesthesia, but died on the second postoperative day from congestive heart failure. Autopsy revealed the heart as the seat of a moderate degree of mitral stenosis, with dilatation of both auricles and the right ventricle of the chronic endocarditic type, while the liver, in addition to moderate chronic passive congestion, showed advanced central necrosis of the hepatic cords not seen in the livers of patients with typical congestive heart failure. Also, there was a significant degree of periportal fibrosis as well as a moderate amount of fatty degeneration.

CASE 4.—An 8½ year old white girl had suffered from hyperthyroidism for three years and on admission to the hospital had a basal metabolic rate of +52 per cent. She was prepared for operation for a five week period and then subjected to a hemithyroidectomy under cyclopropane and oxygen anesthesia. She died twenty-nine hours after the operation from a typical severe thyroid crisis. Autopsy revealed a liver weighing 850 Gm. It was grossly yellow, with the lobules showing red central zones (and yellow peripheries). Microscopically, the central three fourths of each lobule was involved in a process of acute necrosis, the viable cells being in the periportal area. These cells were markedly laden with fat. Each portal space was approximately twice the usual size, owing to proliferation of the connective tissue and accumulation of lymphocytes (figs. 1 and 2). The heart was slightly enlarged but was otherwise normal. Microscopically, a few interstitial hemorrhages between the muscle bundles were seen.

CASE 5.—A 50 year old white woman had had symptoms of hyperthyroidism for fourteen years. Ten years before her admission to the hospital a subtotal thyroidectomy had been performed, with relief of her symptoms for two years. The hyperthyroidism recurred, however, and one year before admission a second thyroidectomy was performed. The patient was again well until six months before admission, when the same symptoms recurred for the second time. On admission to the hospital her basal metabolic rate was +41 per cent. After appropriate preparation the patient was operated on, under avertin with amylene hydrate and cyclopropane anesthesia. Postoperatively her course was satisfactory until the second day, when her temperature and pulse rate rose, her mental state became confused and mild icterus was apparent. Death occurred in a typical crisis sixty hours after operation. Autopsy revealed a moderate degree of jaundice and a liver which was finely nodular and weighed 1,450 Gm. Microscopically, there were advanced portal cirrhosis and a moderate degree of fatty degeneration of the remaining hepatic cells. No fresh parenchymal necrosis was evident (figs. 3 and 4).

CASE 6.—A 41 year old white woman had a severe toxic nodular goiter. The symptoms were of five months' duration, and on admission the basal metabolic rate was +91 per cent. The patient was prepared for seventy-five days and was operated on under avertin with amylene hydrate and nitrogen monoxide anesthesia. On the first postoperative day she exhibited early signs of bilateral bronchopneumonia. By the thirtieth hour after the operation her condition was critical, and in spite of supportive measures she died sixty hours after the operation. Clinically, the cause of death was thought to be bilateral bronchopneumonia. This impression was confirmed at autopsy. The liver, which weighed 1,600 Gm., was slightly pale and soft. Microscopically, there were morphologic changes consisting in fatty degeneration, atrophy and granular degeneration of the cytoplasm of cells in the central half of each lobule. All of these changes ranged from slight to moderate. No necrotic cells were seen.

## FUNCTIONAL CHANGES

To turn from the anatomic changes noted in the liver in cases of hyperthyroidism to studies of its functional capacity in this condition, several significant contributions deserve consideration. Hirose<sup>6</sup> in 1912 found that patients with hyperthyroidism exhibited a high degree of alimentary galactosuria similar to that occurring with hepatic cirrhosis and catarrhal jaundice. Sanger and Hun<sup>7</sup> in 1922 noted diminished dextrose tolerance in patients with hyperthyroidism and attributed this defect to failure of the liver to store dextrose properly. Youmans and Warfield<sup>8</sup> in 1926 employed the dextrose tolerance and phenoltetrachlorophthalein tests for hyperthyroid persons and found impaired hepatic function in 50 per cent of their entire series. Rowe<sup>9</sup> in 1928, using several types of tests, found impaired hepatic function in patients suffering from hyperthyroidism. Kugelmann<sup>10</sup> in 1930, using the levulose tolerance test, was able to demonstrate impairment of the liver's ability to convert levulose to dextrose in such patients. Heilmeyer<sup>11</sup> in 1931 found the urobilin quotient elevated in 50 per cent of his series of patients with hyperthyroidism. In the following year Lichtman,<sup>12</sup> employing the oxidation of cinchophen as a measure of hepatic function, observed slight to moderate impairment in 16 of 20 cases of hyperthyroidism. Hurxthal<sup>13</sup> in 1933 made use of the cholesterol test to study disease of the thyroid and found low levels in patients with hyperthyroidism, noting that the level of the blood cholesterol was inversely proportional to the basal metabolic rate and the clinical symptoms. Pre-operative preparation was associated with some elevation of the level of blood cholesterol, but this was restored to normal only after operation had relieved the symptoms and had controlled the increased metabolism. Ragins<sup>14</sup> in 1935 found the Takata-Ara reaction positive in 6 of 14 cases,

6. Hirose, M.: Ueber die alimentäre Galaktosurie bei Leberkrankheiten und Neurosen, *Deutsche med. Wchnschr.* **38**:1414, 1912.

7. Sanger, B. J., and Hun, E. G.: Glucose Mobilization Rate in Hyperthyroidism, *Arch. Int. Med.* **30**:397 (Sept.) 1922.

8. Youmans, J. B., and Warfield, L. M.: Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, *Arch. Int. Med.* **37**:1 (Jan.) 1926.

9. Rowe, A. W.: Endocrine Studies: XXXV. Association of Hepatic Dysfunction with Thyroid Failure, *Endocrinology* **17**:1 (Jan.-Feb.) 1928.

10. Kugelmann, B.: Ueber Störungen im Kohlenhydratstoffwechsel beim Morbus Basedow, *Klin. Wchnschr.* **9**:1533 (Aug. 16) 1930.

11. Heilmeyer, L.: Blutfarbstoffwechselstudien, *Deutsches Arch. f. klin. Med.* **171**:515, 1931.

12. Lichtman, S. S.: Liver Function in Hyperthyroidism, *Arch. Int. Med.* **50**:721 (Nov.) 1932.

13. Hurxthal, L. M.: Blood Cholesterol in Thyroid Disease: II. Effect of Treatment, *Arch. Int. Med.* **52**:86 (July) 1933.

14. Ragins, A. B.: Value of Takata and Ara Reaction as Diagnostic and Prognostic Aid in Cirrhosis of Liver, *J. Lab. & Clin. Med.* **20**:902 (June) 1935.

and Maddock, Collier and Pedersen<sup>15</sup> in 1936 used the bromsulphalein test and found an impairment of hepatic function in 8 of 13 cases. In the following year Althausen and Wever,<sup>16</sup> employing the galactose tolerance test, found a decreased tolerance in all cases and interpreted their data as evidence of impairment of the ability of the liver to convert galactose to dextrose in the presence of hyperthyroidism.

The development of the hippuric acid test for liver function as described by Quick<sup>17</sup> and applied to disease of the thyroid by Boyce and McFetridge,<sup>2</sup> Bartels and Perkin<sup>18</sup> and Bartels<sup>19</sup> made the intimate relation between the hyperthyroid state and impaired hepatic function even more apparent. Boyce and McFetridge, emphasizing the need for serial determination of the function of the liver by means of the hippuric acid test, found that the depressed hepatic function averaged 58 per cent of the normal in cases of toxic diffuse goiter at the time of the patient's admission to the hospital. With proper preoperative preparation this value rose to 66.7 per cent. Postoperatively there were a characteristic fall of approximately 6 to 8 per cent and a subsequent rise to 76 per cent of normal by the seventh day. The response of toxic nodular goiters to preoperative therapy was more favorable than that of toxic diffuse goiters, which is the reverse of the findings of Bartels. It is interesting to note that in the control cases, in which hernioplasties and elective appendectomies were performed with ethylene anesthesia, a fall from a preoperative level of 100 per cent to 79 per cent occurred in the first twenty-four hours after operation. Recovery was more prompt in those cases, however, the value reaching 91 per cent of normal by the second postoperative day.

Bartels,<sup>19</sup> in an extensive study of hepatic function in hyperthyroidism, stressed the following points: 1. The impairment of hepatic function is directly proportional to the severity of the hyperthyroidism, as determined by the basal metabolic rates and the clinical evidence as to the seriousness of the operative risk. 2. Only 18 of 148 patients showed normal function by the hippuric acid test. 3. The preoperative prepara-

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15. Maddock, W. G.; Collier, F. A., and Pedersen, S.: *Thyroid Crisis: Its Relation to Liver Function and Adrenalin*, *West. J. Surg.* **44**:513 (Sept.) 1936.

16. Althausen, T. L., and Wever, G. K.: *Galactose Tolerance in Hyperthyroidism*, *J. Clin. Investigation* **16**:257 (March) 1937.

17. Quick, A. J.: *Conjugation of Benzoic Acid with Glycine: A Test of Liver Function*, *Proc. Soc. Exper. Biol. & Med.* **29**:1204 (June) 1932; *The Synthesis of Hippuric Acid: New Test of Liver Function*, *Am. J. M. Sc.* **185**:630 (May) 1933.

18. Bartels, E. C., and Perkin, H. J.: *Liver Function in Hyperthyroidism as Determined by the Hippuric Acid Test*, *New England J. Med.* **216**:1051 (June 17) 1937.

19. Bartels, E. C.: *Liver Function in Hyperthyroidism as Determined by Hippuric Acid Test*, *Ann. Int. Med.* **12**:652 (Nov.) 1938.

tion brought about a good response in hepatic function in cases of toxic diffuse goiter but little or no response in cases of toxic nodular goiter. 4. No correlation could be made between the postoperative rise in temperature and the pulse rate and hepatic function as determined by the hippuric acid test. 5. Finally, the use of a high carbohydrate, low fat diet apparently improved hepatic function, as evidenced by increased excretion of hippuric acid.

The experimental evidence for consideration of the determination of the level of the plasma prothrombin as a measure of hepatic function is as follows: Smith, Warner and Brinkhous<sup>20</sup> were the first to show that after use of ninety minutes of deep chloroform anesthesia as the hepatotoxin there was a precipitous fall in the level of plasma prothrombin to less than 10 per cent of normal in twenty-four hours and that the return to normal was not complete until six or seven days had elapsed. Warner,<sup>21</sup> after removing approximately 65 per cent of the liver of the rat, demonstrated a fall in the level of plasma prothrombin to 40 per cent of normal and a return to normal in about two and a half weeks. Lord<sup>22</sup> recently has shown that even gentle massage of the liver for twenty-five minutes produces a fall of 25 per cent in the level of plasma prothrombin, which is recovered from after six days. Andrus, Lord and Moore<sup>23</sup> and Warren and Rhoads<sup>24</sup> have performed total hepatectomy in the dog and observed a precipitous fall in the level of plasma prothrombin to less than 20 per cent of the normal within ten hours. All of the aforementioned workers, with the exception of Warren and Rhoads, employed the two stage titration method of Warner, Brinkhous and Smith<sup>25</sup> for the determination of the plasma prothrombin content. Warren and Rhoads made use of Quick's method.<sup>26</sup>

20. Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), *J. Exper. Med.* **66**:801 (Dec.) 1937.

21. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, *J. Exper. Med.* **68**:831 (Dec.) 1938.

22. Lord, J. W., Jr.: The Effect of Trauma to the Liver on the Plasma Prothrombin: An Experimental Study, *Surgery* **6**:896 (Dec.) 1939.

23. Andrus, W. DeW.; Lord, J. W., Jr., and Moore, R. A.: The Effect of Hepatectomy on the Plasma Prothrombin and the Utilization of Vitamin K, *Surgery* **6**:899 (Dec.) 1939.

24. Warren, R., and Rhoads, J. E.: Hepatic Origin of Plasma-Prothrombin: Observations After Total Hepatectomy in the Dog, *Am. J. M. Sc.* **198**:193 (Aug.) 1939.

25. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, *Am. J. Physiol.* **114**:667 (Feb.) 1936.

26. Quick, A. J.: On Various Properties of Thromboplastin (Aqueous Tissue Extracts), *Am. J. Physiol.* **114**:282 (Jan.) 1936.

From the foregoing observations it would seem evident that the liver is the site of formation of plasma prothrombin and that injury to the liver of varying degrees of severity is followed by a comparable fall in the prothrombin content of the plasma. Clinically, it has been repeatedly noted (Brinkhous and others;<sup>27</sup> Quick;<sup>28</sup> Butt, Snell and Osterberg,<sup>29</sup> Stewart and Rourke;<sup>30</sup> and Andrus and Lord<sup>31</sup>) that in diseases of the liver, such as cirrhosis and catarrhal jaundice, the level of plasma prothrombin is reduced and the response to vitamin K therapy is sluggish or absent.

The only previous reports of which we are aware recommending use of the level of plasma prothrombin as determined by the Warner, Brinkhous and Smith test for the estimation of hepatic function are those of Wilson,<sup>32</sup> published during the past year and a half. He found in a series of 41 patients that there was close correlation between the result of the hippuric acid test and the level of plasma prothrombin as independent measures of hepatic function. Such correlation was lacking when the galactose tolerance test was employed, as the result was normal for all of the patients studied. Wilson remarked that "in two patients with severe cirrhosis of the liver and a consistently low plasma prothrombin level of 23 and 29 per cent respectively, the hippuric acid excretion in one was only 1.2 grams, and in the other 1.9 grams, and large amounts of Vitamin K and bile salts were without demonstrable effect on the prothrombin."

We have recently reported on the use of the response of the plasma prothrombin to intramuscular injections of 2-methyl-1, 4-naph-

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27. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula: Effect of Feeding Bile and Alfalfa (Vitamin K), *Am. J. M. Sc.* **196**:50 (July) 1938.

28. Quick, A. J.: The Nature of the Bleeding in Jaundice, *J. A. M. A.* **110**:1658 (May 14) 1938.

29. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, *J. A. M. A.* **113**:383 (July 29) 1939.

30. Stewart, J. D., and Rourke, G. M.: Prothrombin and Vitamin K Therapy, *New England J. Med.* **221**:403 (Sept. 14) 1939.

31. Andrus, W. DeW., and Lord, J. W., Jr.: Correction of Prothrombin Deficiencies by Means of 2-Methyl-1-4-Naphthoquinone Injected Intramuscularly, *J. A. M. A.* **114**:1336 (April 6) 1940; Clinical Investigations of Some Factors Causing Prothrombin Deficiencies, *Arch. Surg.* **41**:596 (Sept.) 1940; The Use of Intramuscular Injections of 2-Methyl-1, 4-Naphthoquinone in the Treatment of Prothrombin Deficiencies, *Ann. Surg.* **112**:783 (Oct.) 1940.

32. Wilson, S. J.: Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Humans, *Proc. Soc. Exper. Biol. & Med.* **41**:559 (June) 1939; Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Human Subjects, *J. Lab. & Clin. Med.* **25**:1139 (Aug.) 1940.



thoquinone to differentiate intrahepatic jaundice from extrahepatic jaundice.<sup>33</sup> In a series of 10 patients with intrahepatic jaundice, all had reduced levels of plasma prothrombin as determined by the method of Warner, Brinkhous and Smith, the limits being 41 per cent and 76 per cent of normal. After the injection of 2 mg. of 2-methyl-1, 4-naphthoquinone, in no instance did the plasma prothrombin content rise more than 10 per cent. On the other hand, in 18 cases of extrahepatic jaundice the plasma prothrombin response to 2 mg. of 2-methyl-1, 4-naphthoquinone ranged between the limits of + 8 per cent and + 62 per cent of normal. We therefore felt that, although the initial level of plasma prothrombin might be low for several reasons (dietary insufficiency of vitamin K; poor intestinal absorption of vitamin K) and hence might not be a measure of hepatic function in many cases, the response of a lowered level of plasma prothrombin to intramuscular injection of 2-methyl-1, 4-naphthoquinone is a most sensitive measure of hepatic function.

We have followed the levels of plasma prothrombin in a series of cases of hyperthyroidism in the surgical pavilions of the New York Hospital, including 36 cases of toxic diffuse and toxic nodular goiter. No deaths occurred during the period of study. As controls we have followed (1) 10 patients with nontoxic goiter; (2) 10 patients who had undergone hernioplasties, the majority having been done with local anesthesia; (3) 9 patients who had been subjected to major intra-abdominal operations but in whom the liver had not been handled mechanically, and (4) 5 patients who had undergone operations on the brain.

From a study of these cases the following facts emerge. First, the level of plasma prothrombin in cases of preoperative hyperthyroidism shows no direct correlation with the severity of the hyperthyroidism, with the duration of the illness or with the age or sex of the patient. Likewise, the type of goiter, toxic diffuse or toxic nodular, bore no relation to the level of plasma prothrombin. However, what is apparent and perhaps more significant in the consideration of hepatic function in the patient with hyperthyroidism is the behavior of the plasma prothrombin after an operation on the thyroid gland. Post-operatively a significant fall occurred in 29 of 36 cases of toxic goiter, the degree of fall being closely correlated with the severity of the postoperative course as evidenced by the rise in temperature, the pulse rate and the clinical appearance. It happens that there was neither a

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33. Lord, J. W., Jr., and Andrus, W. DeW.: The Differentiation of Intra-hepatic and Extrahepatic Jaundice: The Response of the Plasma Prothrombin to Intramuscular Injection of 2-Methyl-1,4-Naphthoquinone as a Diagnostic Aid. *Arch. Int. Med.*, to be published.

death nor a postoperative crisis in this series, but the level of plasma prothrombin fell to 50 per cent or lower in 6 cases.

Figure 5 shows a composite curve of the plasma prothrombin in 36 cases of toxic goiter and in 10 cases of nontoxic goiter. It is of interest to note that, although there was no significant fall in the postoperative level of plasma prothrombin in the cases of nontoxic goiter, there was a postoperative rise toward a normal level of plasma prothrombin from a slightly reduced preoperative level. In contrast, the curve for toxic goiter showed slight improvement with preoperative therapy from 87 per cent to 92 per cent of normal, and after operation

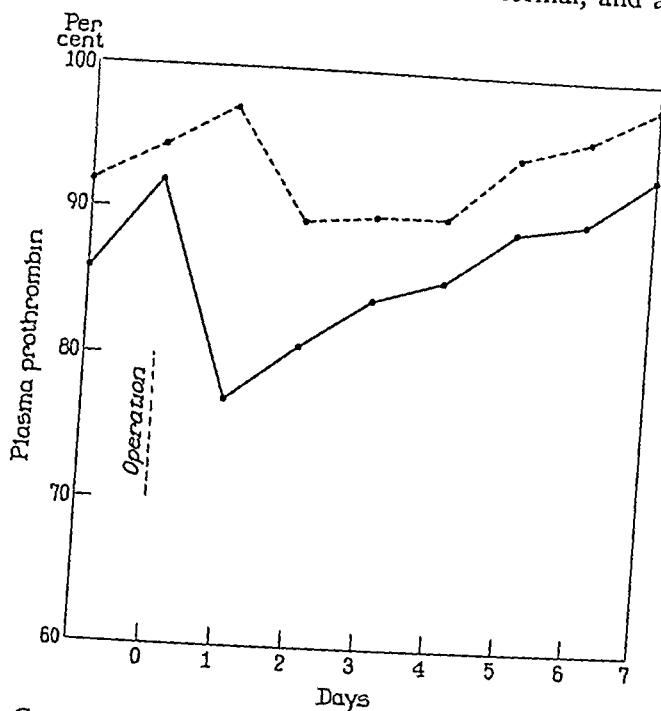


Fig. 5.—Composite curves for average levels of plasma prothrombin in 10 cases of nontoxic goiter (broken line) and 36 cases of toxic goiter (unbroken line).

a precipitate fall occurred in twenty-four hours to 77 per cent, with a subsequent return toward the normal, the level at the end of seven days being 93 per cent.

The aforementioned findings are in marked contrast to the studies on the control group. In the group of patients who underwent major abdominal operations no postoperative fall occurred. Likewise, in a group of 5 patients who underwent operations on the brain, in which moderately prolonged hyperpyrexia followed operation, an average fall of 6 per cent occurred during the first twenty-four hours, with a return to normal by the fourth postoperative day. From this it is evident that fever alone cannot explain the fall in concentration of plasma pro-

thrombin which is observed so frequently and to such a marked degree in the patients with toxic disease of the thyroid. Nine of the 10 patients on whom hernioplasties were performed showed no postoperative fall in the level of plasma prothrombin. The tenth patient, who was operated on with local anesthesia (1 per cent procaine hydrochloride), showed a moderate degree of shock during operation, with a fall in blood pressure from 125 systolic and 75 diastolic to 80 systolic and 58 diastolic, with marked apprehension and cold, sweaty skin. The patient responded promptly to the usual treatment with morphine, heat and an intravenous infusion of dextrose in saline solution. Three hours later the blood pressure was 125 systolic and 58 diastolic. The level of plasma prothrombin two hours after the operation was 50 per cent, but by the twenty-fourth hour this had risen to 90 per cent and by the forty-eighth

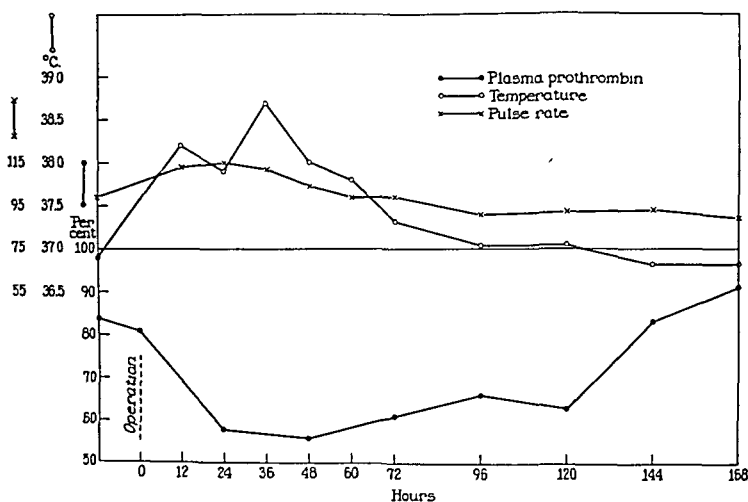


Fig. 6.—Composite curve for average levels of plasma prothrombin in 7 cases of toxic goiter.

hour to 100 per cent, indicating that no such prolonged effect was occasioned as was seen in the patients with toxic diseases of the thyroid.

Figure 6 is a composite chart of seven of the more severe postoperative reactions in the cases of hyperthyroidism studied. The fall in plasma prothrombin is correlated with the postoperative temperature and pulse rate. It is evident that the fall occurred concomitantly with the rise in the pulse rate and temperature but that full recovery in hepatic function lagged behind the return of the temperature and pulse rate toward normal. Figure 7 shows similar data on 1 case of moderately severe hyperthyroidism. The patient in this case had a basal metabolic rate on admission of +75 per cent, which fell to 38 per cent during the preoperative stay in the hospital.

Attempted correlation of the levels of plasma prothrombin with the result of the hippuric acid excretion test was carried out in only a few cases. One of these is illustrative of the possible lack of correlation between the results of the two tests. The patient was a 37 year old white woman whose symptoms were of only six weeks' duration. On admission to the hospital the basal metabolic rate was  $+80$  per cent, and after one month of therapy it was  $+51$  per cent. Bilateral pole ligations carried out in two stages were performed, and three weeks later a determination of the hippuric acid excretion yielded a value of 3.54 Gm., at which time her basal metabolic rate was  $+60$  per cent. Four weeks later, before the first stage of the hemithyroidectomy, the value for hippuric acid excretion was 4.7 Gm. and the value for plasma

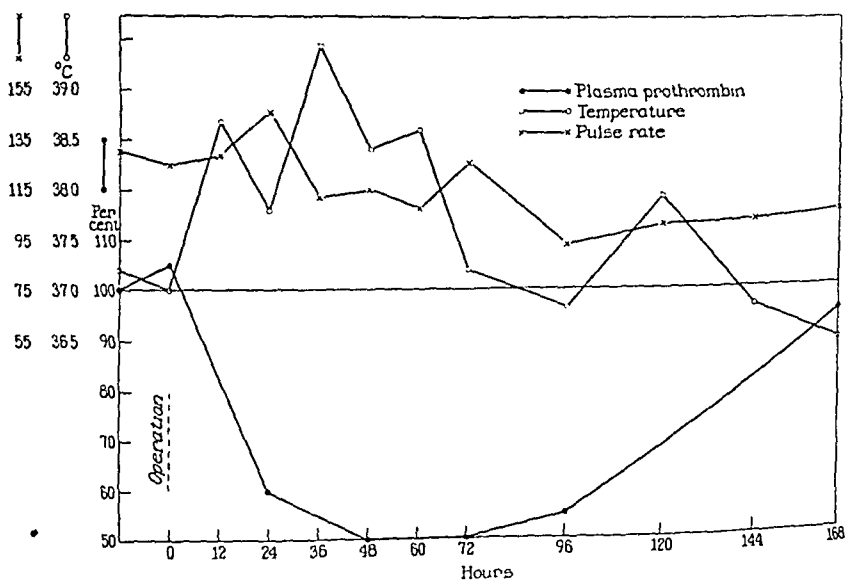


Fig. 7.—Correlation of the curve for plasma prothrombin with the postoperative reaction in a case of moderately severe hyperthyroidism. The patient was a woman aged 34 who had a toxic goiter.

prothrombin 100 per cent. However, postoperatively the plasma prothrombin fell to 50 per cent, and it had returned to only 85 per cent of normal by the sixth postoperative day. It would seem that in spite of an apparently normally functioning liver as determined by the hippuric acid test the strain of a partial thyroidectomy caused definite and significant impairment of hepatic function as determined by the level of plasma prothrombin.

Recently, a patient with a toxic diffuse goiter had marked clinical jaundice (icteric index, 50) following first stage hemithyroidectomy with local anesthesia. The temperature, the pulse rate and the patient's appearance, however, did not suggest a real crisis. Nevertheless, the

plasma prothrombin fell from a preoperative level of 61 per cent to 43 per cent of normal on the first day and 28 per cent on the third day after the operation. A subsequent rise to 60 per cent had occurred by the sixth day. The marked drop in plasma prothrombin concentration is highly suggestive of a severe degree of temporary hepatic impairment.

## COMMENT

The accumulated evidence of the anatomic and functional changes in the liver in cases of hyperthyroidism suggests strongly an intimate relation between functional or even morphologic changes in the liver and severe postoperative hyperthyroid storm. How the marked pathologic changes of acute parenchymatous degeneration and necrosis come about and what causes the remarkable reduction in function as demonstrated by the hippuric acid test and the fall in the level of plasma prothrombin following thyroidectomy in cases of hyperthyroidism has not been explained. However, various factors, such as the increased metabolic demands of the body in the presence of hyperthyroidism, the decreased dextrose tolerance, the influence of a high caloric diet if this is high in fat and the postoperative febrile reaction, may all tend to increase the susceptibility of the liver to injury. Whether there is actually a circulating agent which is hepatotoxic or whether the aforementioned factors in combination are responsible for the hepatic damage cannot be answered at present. Rich<sup>34</sup> has shown experimentally that damage to the liver results when anoxemia and fever occur concomitantly. Although anatomic changes in the liver have been produced in rats, cats and rabbits<sup>35</sup> by feeding large amounts of thyroid, Youmans and Warfield<sup>8</sup> were unable to detect impairment of hepatic function in dogs with hyperthyroidism. On the other hand, Drill and Hays<sup>36</sup> have recently produced impairment of hepatic function as determined by the bromsulphalein test in dogs fed thyroid (0.6 Gm. per kilogram per day). They found that a diet adequate in yeast prevented the impairment of hepatic function and that it was the lack of yeast in the diet which led to the functional change. The foregoing findings are of great significance when considered in the light of the recent work

34. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, *Bull. Johns Hopkins Hosp.* **47**:338 (Dec.) 1930.

35. Hashimoto, H.: The Heart in Experimental Hyperthyroidism, with Special Reference to Its Histology, *Endocrinology* **5**:579 (Sept.) 1921. Farrant, R.: Hyperthyroidism: Its Experimental Reproduction in Animals, *Brit. M. J.* **2**:1363, 1913. Gerlei, F.: Nécrose du foie consécutive à l'empoisonnement par la thyroxine, *Ann. d'anat. path.* **10**:555 (May) 1933.

36. Drill, V. A., and Hays, H. W.: Hyperthyroidism and Liver Function in Relation to B Vitamins, *Proc. Soc. Exper. Biol. & Med.* **43**:450 (March) 1940.

by Rich and Hamilton<sup>37</sup> on the production of cirrhosis of the liver in rabbits by the deprivation of an unknown factor in the vitamin B complex. It would therefore seem advisable from the experimental evidence to supplement the diet of the patient with hyperthyroidism by administration of adequate amounts of the B complex.

#### SUMMARY

The important historical evidence of the morphologic damage to the liver accompanying hyperthyroidism is outlined.

In the New York Hospital series of 680 operative patients with hyperthyroidism, 16 died after operation and 6 came to autopsy. The pathologic changes in the liver are described.

The historical evidence of the impairment of hepatic function associated with hyperthyroidism is reviewed.

A series of 36 consecutive patients with hyperthyroidism and 34 controls have been studied by means of the level of plasma prothrombin as determined by the Warner, Brinkhous and Smith test. Impairment of hepatic function was noted following operation in 29 of the 36 patients in the former group.

The influence of the carbohydrate-fat ratio of the diet and of the vitamin B complex on the liver is discussed.

It is suggested that in the preparation for operative treatment of the patient with hyperthyroidism a high caloric, high carbohydrate, high protein, low fat diet supplemented with liberal amounts of vitamin B complex should be employed.

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37. Rich, A. R., and Hamilton, J. D.: Experimental Production of Cirrhosis of the Liver by Means of a Deficient Diet, *Bull. Johns Hopkins Hosp.* **66**:185 (March) 1940.

# PULMONARY EMBOLISM

AN EXPERIMENTAL STUDY OF VARIATIONS IN THE VOLUME  
BLOOD FLOW IN THE INFERIOR VENA CAVA OF THE DOG

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AND

SIDNEY SMITH, M.S.

CHICAGO

In a publication<sup>1</sup> on the prevention of pulmonary embolism some clinical evidence was brought forth to support the thesis that postoperative exercises are beneficial in preventing venous thrombosis. It was assumed that simultaneous deep breaths and active leg exercises taken at regular intervals would vary the blood flow in the pelvic venous cistern and "wash out" any accumulation of blood elements which might lead to beginning formation of thrombi. Although it was definitely stated in this publication that coincidence may have been a factor, in approximately 500 cases in which the patients took postoperative exercises there was no thrombophlebitis or pulmonary embolism. In 95 control cases of fractures of the back, pelvis, hip, femur or leg requiring complete immobilization there were 5 cases of thrombophlebitis, in 3 of which there were pulmonary emboli.

It is recognized that clinical application of a principle should follow experimental studies rather than deductive reasoning. For years postoperative activity has been widely advocated but only sporadically pursued. To determine whether the reasoning back of the clinical application of postoperative exercises could be substantiated, a series of simple experiments were performed on 6 dogs. Variations in the volume flow of blood in the inferior vena cava were measured with a venturimeter. Since the results were the same in all animals, further repetition was deemed unnecessary.

## APPARATUS<sup>2</sup>

The Venturi principle was employed in these experiments by producing partial constriction of a stiff rubber tube connected with the cut ends of the inferior vena cava (fig. 1). A "T" tube was inserted into each end of this rubber tube,

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From the Department of Surgery of Rush Medical College of the University of Chicago.

1. Potts, W. J.: Pulmonary Embolism, *Ann. Surg.* **111**:554 (April) 1940.

2. This apparatus was perfected by Dr. Joseph Holt, of the department of physiology of the University of Chicago, who permitted its use in this study.

and to the vertical ends of the T tubes an inverted glass U tube, or differential manometer, was connected with fine, stiff rubber tubing. Variations in the height of the fluid level produced by changes in volume flow in the inferior vena cava were read from this differential manometer and by means of a hand-worked device were recorded on a smoked drum.

A pressure bottle containing sodium citrate was connected with finely drawn glass tubing to each rubber tube leading to the differential manometer. A constant fine stream of the citrate solution was thereby continuously forced toward the blood stream to prevent blood from coming into and clogging the apparatus.

It is essential that all rubber tubing be of the stiff, nonexpansile type and that all connections be absolutely tight. There must be no air in the apparatus

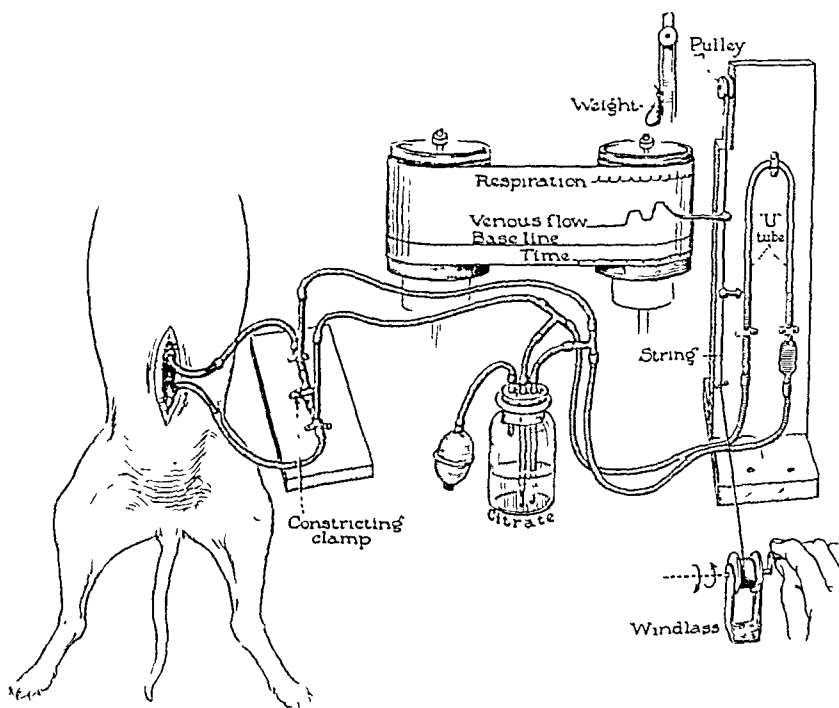


Fig. 1.—Diagrammatic sketch of apparatus.

except in the inverted U tube. The constricting clamp applied between the T tubes must be adjusted so as to produce the proper variation in the water levels in the differential manometer and must not be changed during the experiment.

By attaching the T tubes to a block fixed to the table the mechanics of the experiment were simplified and uncontrollable factors were eliminated.

A pneumograph was attached to the dog's chest, and respirations were recorded on the smoked drum exactly above the graph of blood flow.

#### PROCEDURE

The dog was anesthetized with pentobarbital sodium given intravenously. A cannula was introduced into the trachea to allow unobstructed breathing. The abdomen was opened in the midline and the inferior vena cava exposed from the junction of the iliac veins to the renal veins. All small veins emptying into this portion of the vena cava were tied. At this point an anticoagulant consisting



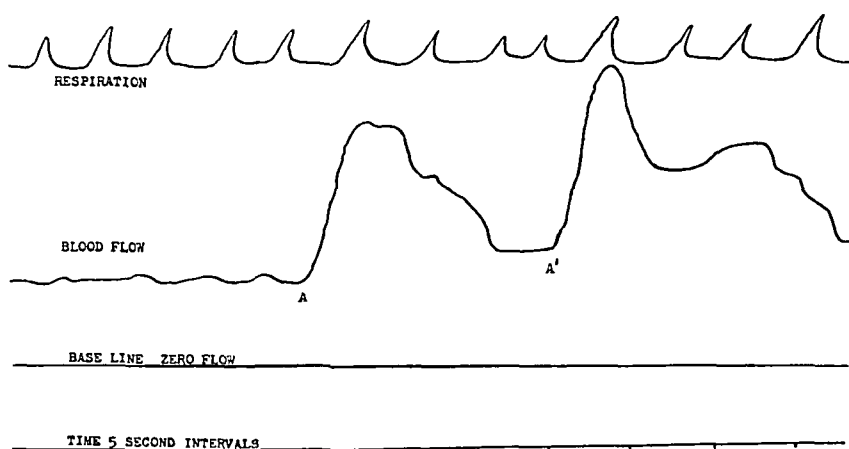


Fig. 2.—*A*, effect of elevation of both hindlegs. *A'*, effect of elevation of both hindlegs and simultaneous contraction of the leg muscles.

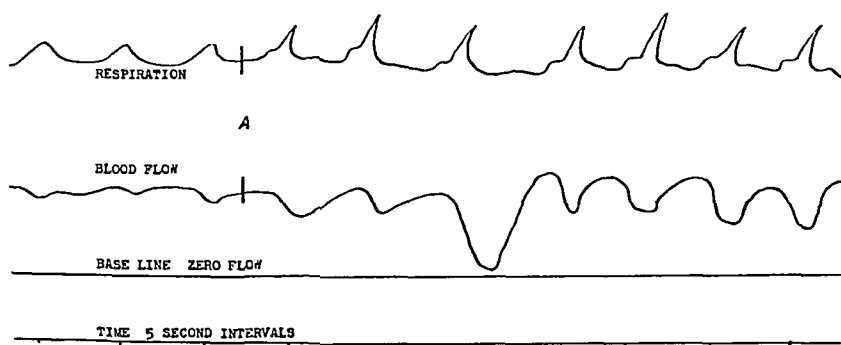


Fig. 3.—Effect of deep respirations produced with carbon dioxide inhalations begun at point *A*.



Fig. 4.—*A* and *A'*, curve with the lungs overinflated and the respirations forcibly stopped. *B*, effect of elevation of both hindlegs simultaneous with release of overinflated lungs.

of 100 mg. of chlorazol fast pink BKS<sup>3</sup> (trade name, fastusol pink) per kilogram of body weight was injected intravenously. Curved glass tubes the size of the inferior vena cava were inserted, one into the proximal and the other into the distal portion of the vessel. These were connected to the T tubes.

#### EXPERIMENTS

Simultaneous elevation of both hindlegs of the dog produced an increase varying from 100 to 150 per cent in the volume flow of blood in the inferior vena cava (fig. 2). In animals rather lightly anesthetized, contraction of the muscles in both hindlegs occurring coincident with their elevation produced an increase of more than 250 per cent in the volume flow (fig. 2). The increase in the volume flow was abrupt and returned to normal in ten to fifteen seconds. To check the accuracy of our observations, the femoral veins were isolated just below the inguinal ligament and clamped. Elevation of the legs then produced practically no change in the volume of blood flow. Removal of the clamps was followed by a prompt increase in flow.

Normal respiration caused little demonstrable alteration in blood flow. Deep respirations, however, produced by inhalation of carbon dioxide caused irregular changes in flow (fig. 3).

It has been shown by Luckhardt, Alpert and Smith<sup>4</sup> that the reflex inhibition of respiration will temporarily obstruct the return flow of blood to the heart. The longer the breath is held the greater will be the damming back of the venous blood. To simulate this condition the dog's lungs were overinflated by blowing on the tracheal cannula and then occluding it. Blood flow in the inferior vena cava dropped to almost zero. Release resulted in a prompt and marked rise in blood flow (fig. 4). Simultaneous elevation of the hindlegs, with deflation of the overinflated lungs, caused an enormous increase in blood flow (fig. 4).

Calibration of the blood flow in cubic centimeters in the inferior vena cava under normal and experimental conditions was determined but is of no interest here. We sought only to determine the *variations* in the volume of blood flow which could be produced.

#### CONCLUSION

Experimentally we have shown that breathing and leg exercise cause great variations in the volume blood flow in the inferior vena cava. Clinically we believe that deep breathing and leg exercise are of value in preventing postoperative thrombosis and pulmonary embolism.

3. Modell, W.: Chlorazol Fast Pink BKS as an Anticoagulant, *Science* **89**: 349 (April 14) 1939.

4. Luckhardt, A. B.; Alpert, R., and Smith, S.: Hemodynamic and Respiratory Changes Following the Manipulation and Traction of the Gastrohepatic Ligament, *Science* **76**:545 (Dec. 9) 1932.

# MACROSCOPICALLY NONPATHOLOGIC GALLBLADDER

## A CLINICOPATHOLOGIC STUDY

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ROCHESTER, MINN.

More than three fourths of all gallbladders removed contain stones, which are thought by many to cause symptoms invariably.<sup>1</sup> Removal of the gallbladder results in relief of symptoms in 90 to 95 per cent of cases.<sup>2</sup> Gross disease of the gallbladder without stones, so-called acalculous cholecystitis, also probably causes symptoms in the majority of cases, and removal of the organ is attended by relief of symptoms in 80 to 90 per cent.<sup>2a</sup> A third type of gallbladder occasionally encountered at operation for clinically diagnosed disease of the gallbladder contains neither stones nor any other macroscopic evidence of disease. It is this type of gallbladder with which the present report is concerned. Judd and his associates have remarked, "such cases constitute one of the major therapeutic problems of biliary surgery."<sup>2a</sup> Although results in the individual case are unpredictable, it has been found empirically that removal of such a normal-appearing gallbladder results in relief of symptoms in only a slightly smaller percentage of cases than in either of the two groups aforementioned. The problems of preoperative diagnosis of such a condition and, when it is encountered at the operating table, the problem of determining whether removal of the gallbladder will be in the best interest of the patient prompted the present study.

Included are those patients whose gallbladders were removed by primary cholecystectomy at the Mayo Clinic in the years 1931 to 1933,

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\*Fellow in Surgery, the Mayo Foundation.

Abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

1. Mayo, W. J.: "Innocent" Gallstones a Myth, J. A. M. A. **56**:1021-1024 (April 8) 1911. Walters, W.; Gray, H. K., and Priestley, J. T.: Surgical Report for 1938 on Lesions of the Stomach and Duodenum, Proc. Staff Meet., Mayo Clin. **14**:807-814 (Dec. 20) 1939.

2. (a) Judd, E. S.; McIndoe, A. M., and Marshall, J. M.: Surgery of the Biliary System, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1931, vol. 7, chap. 2. (b) Snell, A. M.: Diseases of the Gallbladder and Bile Ducts, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1936, vol. 3, chap. 7, pt. 2, pp. 433-472.

inclusive, and on examination in the laboratory revealed grossly a minimum of pathologic change. Among these patients, of course, are some for whom the appendix was incidentally removed at the time of primary cholecystectomy. This period represents a follow-up interval of at least five years, a sufficient postoperative interval to discount properly the benefits obtained from prolonged rest in bed, supervised convalescence, nutritious diet and so forth. Of the 1,981 gallbladders removed in this period, 81.9 per cent contained stones, and these gallbladders plus those with tumors or macroscopic deposits of cholesterol ("strawberry gallbladder") and those on which previous operation had been done were eliminated from this study, as were also those with abnormally thick walls and those that were unduly distended or markedly atrophic. Of the remaining 114 (5.75 per cent), which were to all intents and purposes normal, thin-walled gallbladders, 10 were not included in this study because of the coexistence of other abdominal

TABLE 1.—*Relative Incidence of Signs and Symptoms in One Hundred and Four Cases*

Signs and Symptoms	Number	Percentage
History of pain .....	88	84.6
History of colic .....	33	31.7
History of jaundice .....	31	29.8
Clinically typical of cholecystitis.....	54	51.9
Nervousness .....	49	47.1
Tenderness, epigastric or in right upper quadrant.....	67	64.4
History of typhoid fever.....	15	14.4

pathologic conditions or because of former operations which might have been reflected in the clinical course. The remaining 104 of the 114 form the basis of this report. The histories were reviewed for correlation of the symptoms, the operative findings and the pathologic change, and the results were determined through correspondence.

#### PREOPERATIVE FINDINGS

*Age and Sex.*—The average age of the patients was 41.2 years. There were 76 women, ranging from 21 to 64 years of age, and there were 28 men, ranging from 21 to 61 years of age.

*Signs and Symptoms.*—The average duration of symptoms was six and two-tenths years. Twenty-four patients had had symptoms for one year or less. Twenty-two had had reasons for complaint for ten years or longer. Pain, either epigastric or in the right upper quadrant of the abdomen was the most common single symptom (table 1). In many cases it was typical of biliary colic. Only half of the patients had

symptoms thought to be typical of disease of the gallbladder. In 2 who had a history of jaundice, clinical jaundice was present at the time of examination (tables 1 and 2). In the cases of 7 others a history suggestive of jaundice (dark urine, light stools and pruritus) was obtained. Those with evidence of either definite neurosis or nervous exhaustion (11 men and 38 women) comprised roughly half of any group considered, regardless of whether they were grouped according to age, according to sex or according to clinical history. A history of antecedent typhoid fever was noted for 21 to 28 per cent of persons with disease of the gallbladder in general, although recovery of the specific organism was rarely made.<sup>3</sup> Such a history was noted in only 8.5 per cent of one large series of routine necropsies.<sup>4</sup> In studies of noncalculous disease of the gallbladder the incidence has been reported as 5.53 per cent<sup>5</sup> and 7.1 per cent,<sup>6</sup> respectively. In the present study 4 men and 11 women gave a history of typhoid fever. Forty-three (56.6 per cent) of the women had been pregnant, with an average of three and six-tenths

TABLE 2—*Findings Associated with a History of Jaundice in Thirty-One Cases*

Findings	Cases	Percentage
History of pain . . . . .	28	90.3
Pain and tenderness ..	18	58.1
Hepatitis (surgical) ... .	18	58.1
Pancreatitis (surgical) .	7	22.6
History of typhoid fever .	7	22.6

pregnancies each. More than half of the patients (53) had undergone previous abdominal surgical procedures, 48 (90 per cent) of which were appendectomies. Appendectomy and cholecystectomy had been done in 43 cases, leaving only 13 in which the appendix had not been removed.

*Cholecystography.*—Cholecystograms (oral) were made in 87 cases.<sup>7</sup> Of these, in almost 90 per cent normally functioning gallbladders were seen. In 3 of these cases the report was "with stones," although no stones were found at operation, an error of 3.4 per cent. Almost all

3. (a) Blalock, A.: A Clinical Study of Biliary Tract Disease, J. A. M. A. **83**:2057-2060 (Dec. 27) 1924. (b) Ivy, A. C., and Sandblom, P.: Biliary Dyskinesia, Ann. Int. Med. **8**:115-122 (Aug) 1934. (c) Judd, E. S.: Cholecystitis, Northwest Med. **25**:167-171 (April) 1926.

4. Mentzer, S. H.: A Clinical and Pathologic Study of Cholecystitis and Cholelithiasis, Surg., Gynec. & Obst. **42**:782-793 (June) 1926.

5. Deaver, J. B., and Bortz, E. L.: Gallbladder Disease: A Review of Nine Hundred and Three Cases, J. A. M. A. **88**:619-623 (Feb. 26) 1927.

6. Muller, G. P.: The Noncalculous Gallbladder, J. A. M. A. **89**:786-789 (Sept. 3) 1927.

7. Kirklin, B. R.: Persisting Errors in the Technic of Oral Cholecystography: A Procedure Designed to Avoid Them, J. A. M. A. **101**:2103-2105 (Dec 30) 1933

(91.6 per cent) of the patients with a history of colic were found to have normal roentgenograms. Of those with normal cholecystograms, 28.7 per cent gave a history of colic. Because a gallbladder may be so damaged at one time as to be nonfunctioning and yet recover sufficiently to fill, concentrate and empty normally at a later date,<sup>8</sup> the diagnosis should not rest entirely on a cholecystographic report.<sup>2</sup>

#### OPERATIVE FINDINGS

*Adhesions.*—The frequency of adhesions around the gallbladder in association with disease of the biliary tract in general has been found to run as high as 73 per cent.<sup>9</sup> A relatively avascular peritoneal fold, described by Nagel as the "cholecystoduodenocolic fold," joins the gallbladder and the duodenum normally in 12.5 per cent of cases.<sup>10</sup> In the present study a third (35) of the patients had adhesions around the gallbladder. An attempt to correlate the symptoms with the operative findings was discouraging.<sup>11</sup> A history of either pain or colic was more frequent among patients without adhesions (88.4 per cent and 34.7 per cent, respectively) than among those with adhesions (77.1 per cent and 25.7 per cent, respectively), which absolves the adhesions from being the primary cause of either. Nor could the adhesions be attributed to previous abdominal operations, for adhesions were as frequent among those who had not had the abdomen opened previously (37.3 per cent) as among those on whom operations previously had been performed (30.2 per cent). Adhesions in the former group were probably inflammatory in origin, except for those which were due to rare congenital anomalies. Adhesions did not affect the cholecystograms, for more than 90 per cent of patients with adhesions had a normally functioning gallbladder, even a higher percentage of normal gallbladders than was noted among those with no adhesions. This supports Kirklin's statement that adhesions around the gallbladder cannot be accurately diagnosed cholecystographically.

8. Murphy, G. T., and Bollman, J. L.: The Concentrating Activity of Bile in the Gallbladder Following Restoration from Acute Experimental Cholecystitis, *S. Clin. North America* **11**:917-919 (Aug.) 1931.

9. (a) Brown, M. J.: Non-Calculous Chronic Gall-Bladder Disease, *Am. J. Surg.* **41**:238-254 (Aug.) 1938. (b) Carman, R. D.; MacCarty, W. C., and Camp, J. D.: Roentgenologic Diagnosis of Cholecystic Disease, *Radiology* **2**:80-89 (Feb.) 1924. Blalock.<sup>3a</sup>

10. Nagel, G. W.: The Etiology and Importance of the Cystico-Duodeno-Colic Fold, *Surg., Gynec. & Obst.* **37**:365-372 (Sept.) 1923.

11. (a) Behrend, A., and Gray, H. K.: Acute Cholecystitis: Problems Created by an Attempt to Correlate Its Clinical, Surgical and Pathologic Manifestations, *Surgery* **3**:195-199 (Feb.) 1938. (b) Mayo, W. J.: Cholecystitis Without Stones or Jaundice in Its Relation to Chronic Pancreatitis, *Am. J. M. Sc.* **147**:469-474 (April) 1914. (c) Snell.<sup>2b</sup>

*Hepatitis and Pancreatitis.*—Many investigators have concluded that infiltration of the portal spaces by leukocytes can be demonstrated frequently both at operation and at necropsy, regardless of the presence or absence of biliary disease.<sup>12</sup> Such hepatitis has no clinical significance, is of little importance in the production of symptoms<sup>13</sup> and is not a factor in causing clinical cirrhosis.<sup>12a, b</sup> Even those who contend that there is a relation between cholecystitis and hepatitis fail to agree as to which is primary.<sup>14</sup> In the present study, 51 patients (49 per cent) were described by the surgeon as having hepatitis, although for none of these was the diagnosis confirmed by biopsy. This so-called hepatitis was almost as frequent among those whose appendixes had been removed (43.7 per cent) as among those who still had their appendixes when examined (53.6 per cent).

Pancreatitis in cases of "stoneless" cholecystitis has been reported by different observers as occurring in 1.2 per cent<sup>5</sup> and 14.4 per cent of cases.<sup>15</sup> In the present study pancreatitis was reported in 15 cases (14.4 per cent). Enlarged lymph nodes along the cystic and common bile ducts were present in 15 cases (14.4 per cent). The common bile duct was explored and was drained with a T tube in 2 cases. No gross pathologic lesion was found in either the stomach or the duodenum of any patient.

#### PATHOLOGIC PICTURE

The wall of the normal gallbladder varies in thickness from 0.75 mm. in the distended state to 2 or 3 mm. in a state of contraction.<sup>16</sup> Fat in the serosa may increase this thickness and may rob the organ of its bluish appearance, although there is no evidence that this is not a normal condition.<sup>9b</sup> Solitary lymph follicles are found in the bases of the crypts formed by the folds into which the mucous layer is thrown, seemingly by underlying corresponding ridges of connective tissue of

12. (a) Martin, W.: *Hepatitis and Its Relation to Cholecystitis*, Ann. Surg. **85**:535-554 (April) 1927. (b) Noble, J. F.: *The Relation of Hepatitis to Cholecystitis*, Am. J. Path. **9**:473-496 (July) 1933. (c) Mentzer.<sup>4</sup>

13. Snell, A. M.: Personal communication to the author.

14. (a) Graham, E. A.: *Hepatitis: A Constant Accompaniment of Cholecystitis*, Surg., Gynec. & Obst. **26**:521-537 (May) 1918. (b) Matthews, A. A.: *Pathology and Diagnosis of Cholecystitis*, Northwest Med. **25**:171-178 (April) 1926. (c) Rehfuess, M. E., and Nelson, G. M.: *The Problem of Gall-Bladder Infection*, Am. J. Digest. Dis. **5**:571-576 (Nov.) 1938. (d) Wilkie, A. L.: *The Significance of Hepatitis in Relation to Cholecystitis: An Experimental Study*, Brit. J. Surg. **16**:214-220 (Oct.) 1928. (e) Noble.<sup>12b</sup>

15. Hartman, H. R.: *Jaundice in Surgical Cholecystitis Without Stones*, M. Clin. North America **7**:89-95 (July) 1923.

16. Sudler, M. T.: *The Architecture of the Gall-Bladder*, Bull. Johns Hopkins Hosp. **12**:126-129 (April-June) 1901. Carman and others.<sup>9b</sup>

the fibromuscular layer (fig. 1). In this layer of connective tissue there are rich networks of capillaries and lymphatic vessels, although the latter do not extend up into the folds. As a result, materials which pass through the mucosa into the lymphatic vessels must traverse much connective tissue and are probably carried there by the wandering cells of connective tissue. Lymphocytes may be present normally in the wall of the gallbladder even in an infant.<sup>17</sup> With these observations, like Noble one wonders whether many of the minimal cellular reactions seen in gallbladders removed surgically really represent a pathologic process.



Fig. 1.—Solitary lymph follicle of the mucosa at the base of a crypt in a gallbladder which otherwise showed minimal lymphocytic infiltration.

The incidence of disease of the gallbladder as revealed by the microscope at necropsy is variously reported as from 30 to 75 per cent, and some believe that it is doubtful that any person more than 30 years of age can boast of a normal gallbladder.<sup>18</sup>

17. Graham, E. A., and Peterman, M. G.: Further Observations on the Lymphatic Origin of Cholecystitis, Choledochitis and the Associated Pancreatitis, *Arch. Surg.* 4:23-50 (Jan.) 1922. Maximow and Bloom, cited by Noble.<sup>12b</sup>

18. Brown, C. F. G., and Delkart, R. E.: Keto-Cholanic Acids in the Medical Management of Low Grade Gallbladder Disease, *J. A. M. A.* 108:458-461 (Feb. 6) 1937. Mentzer.<sup>4</sup> Carman and others.<sup>9b</sup>



At the time of cholecystectomy these gallbladders were studied grossly and microscopically.<sup>19</sup> Chronic catarrhal cholecystitis of grade 1 or less (on the basis of 1 to 4) was diagnosed in 92 (88.4 per cent); in 4 of these the walls were described as slightly thickened, and pericholecystitis was diagnosed in 2 of them. In 7 (6.7 per cent) cholecystitis of grade 2 was diagnosed, and in 5 (4.8 per cent), subacute cholecystitis; in 1 of these the subacute cholecystitis was said to be superimposed on chronic cholecystitis. The absence of the diagnoses chronic fibrous cholecystitis and "strawberry" gallbladder will be noticed. For the present study, new blocks were taken from two different regions and microscopic sections made of these. The hematoxylin-eosin stain was used. Eight specimens would no longer take stain, even with "rejuvenation"; hence, the microscopic observations and the tabular material are based on 96 from which suitable sections were obtained. All showed

TABLE 3.—*Findings in Relation to the Original Pathologic Diagnosis of Ninety-Six Specimens Reexamined Microscopically*

Original Pathologic Diagnosis	Cases	Lymphocytic Infiltration			
		Minimal		Marked	
		Cases	Percentage	Cases	Percentage
Chronic catarrhal cholecystitis, grade 1 or less.....	84	46	54.8	38	45.2
Chronic catarrhal cholecystitis, grade 2 .....	7	2	28.6	5	71.4
Subacute cholecystitis .....	5	4	80.0	1	20.0
Totals.....	96	52	54.2	44	45.8

some lymphocytic infiltration of the mucosa and muscular layer. These were arbitrarily divided into two groups: 1. Those with few lymphocytes scattered throughout the mucosa and muscle bundles were labeled for the sake of tabulation "minimal infiltration" (fig. 2). 2. Those with many lymphocytes throughout the wall were labeled "marked infiltration" (fig. 3). It was felt that classification into subgroups was impractical. In most of the sections the degree of lymphocytic infiltration in the mucosa was proportional to that in the muscular layer and serosa. In the few instances in which this was not true the degree of lymphocytic infiltration in the muscular layer was taken as the criterion. In most specimens the postoperative changes made impossible the identification of cellular changes in the mucosa, such as edema and degeneration.

Only rarely could a polymorphonuclear leukocyte be demonstrated outside a vessel, and that usually singly, with no other similarly situated

19. Broders, A. C.: Modification of Wilson's Fresh and Frozen Section Technic, J. Lab. & Clin. Med. 16:734-738 (March) 1931.

cell in the section to confirm this observation. Numerous collections of polymorphonuclear leukocytes were seen within thin-walled vessels with relatively large lumens, a form of "margination of leukocytes" in vessels. The operative trauma and blood stasis incident to cholecystectomy doubtless play a large part in this phenomenon. Whether or not there are any cellular changes, either within the vessels or in the tissues of the walls, secondary to the use of dye in cholecystographic procedures I am unable to say. Certain cholecystographic dyes, probably

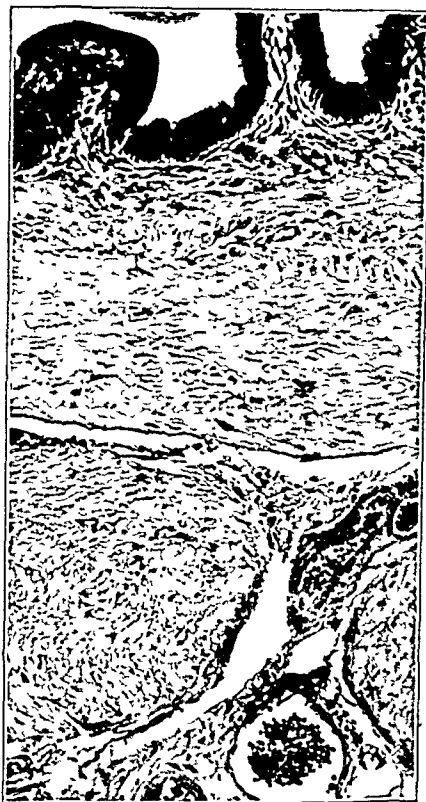


Fig. 2.—Mucosa and muscle layer of a macroscopically nonpathologic gallbladder in which there was minimal lymphocytic infiltration. The scarcity of lymphocytes either in or between the muscle bundles will be noticed.

owing in part to their content of iodine, are bacteriostatic and germicidal,<sup>20</sup> and it is only reasonable to suspect that the irritation produced by such a substance in the gallbladder, especially when concentrated and stored there for twelve to fourteen hours, will result in some signs of inflammation. The findings in the present study offer nothing in

20. Nickel, A. C.: The Bacteriostatic and Germicidal Value of Tetiothalein Sodium—N. N. R. (Tetraiodophenolphthalein), Proc. Staff Meet., Mayo Clin. 4: 178-179 (June 5) 1929.

support of this, however, as almost two thirds of those without the dye showed more than minimal cellular infiltration. Table 3 contains the various findings and a comparison of the microscopic picture with the original pathologic diagnosis. In more than half of the cases only minimal lymphocytic infiltration was present. It seems logical to conclude that chronic catarrhal cholecystitis of grade 1 or 2 and (in some cases) subacute cholecystitis, both either with or without slight thickening of the wall, mean more or less the same thing pathologically, that

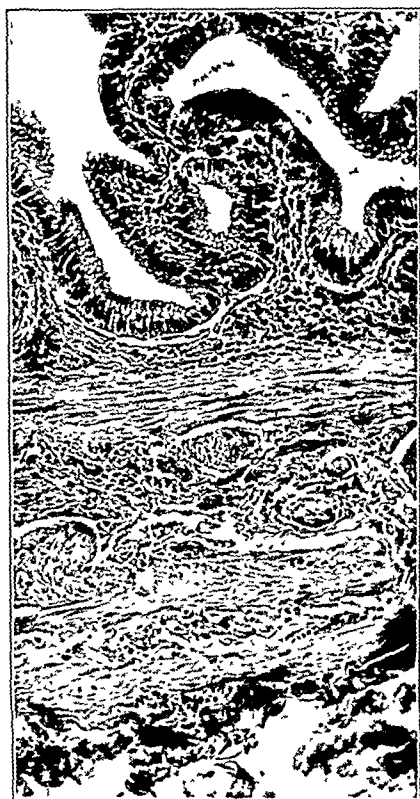


Fig. 3.—Mucosa and muscle layer of a macroscopically nonpathologic gallbladder in which there was marked lymphocytic infiltration. The numerous lymphocytes in and especially between the muscle bundles will be noticed.

is, "not far from normal," especially when these terms are used by different pathologists. It is felt that little additional information can be obtained from the microscopic examination of most gallbladders in which no pathologic condition is evident macroscopically, for all will contain a variable number of lymphocytes in the wall.

On correlation of the microscopic observations with the cholecystograms, the only thing significant is that the majority of the poorly functioning gallbladders as well as the majority of the normally functioning ones showed only minimal lymphocytic infiltration.

There is no relation between the operative findings, such as "hepatitis" and adhesions, and the microscopic pathologic appearance of the gallbladder in these cases. Marked infiltration occurred even more frequently in those without "hepatitis" than in those with this apparent hepatic change. This concurs with the views that Noble has expressed. The same is true in regard to the presence of adhesions and the microscopic picture.

#### MORTALITY

The mortality rate associated with cholecystectomy has been so greatly reduced that the operation is no longer regarded as hazardous. In 930 cases in which all types of cholecystectomy were done at the Mayo Clinic in 1938 the mortality was 1.82 per cent.<sup>1b</sup> The mortality in the present study was 0.96 per cent. The 1 death occurred on the seventh postoperative day, three days after spontaneous opening of

TABLE 4.—*Information Concerning Deaths After Dismissal from Hospital\**

Case	Sex	Age at Operation, Years	Cause of Death	Time of Death, Postoperatively
1	Male	35	Separation of wound.....	7 days
2	Female	57	Coronary occlusion? .....	35 days
3	Female	39	Carcinoma of pancreas.....	8 months
4	Male	42	In course of herniorrhaphy.....	21 months
5	Male	41	Unknown .....	2 years
6	Male	36	Diabetes and pulmonary tuberculosis	28 months
7	Female	55	Carcinoma of bladder.....	51 months
8	Female	34	Anemia; splenomegaly .....	6 years

\* Except for case 1.

the wound following hiccups. Follow-up letters and return visits to the clinic gave information on 91 patients, excluding the single patient who died after the operation. Six of these patients were dead at the end of five years; another died six years after cholecystectomy (table 4). The third patient listed in table 4 died eight months after operation, of carcinoma of the pancreas. This diagnosis was proved at necropsy. When cholecystectomy was done the pancreas was grossly normal, although the spleen was three times the normal size. The patient had had typical biliary colic with symptoms for ten years. It may be argued, and rightly, that the patient's original complaints were due to carcinoma of the pancreas, although we did not feel that a history of complaints extending over ten years was compatible with a diagnosis of carcinoma of the pancreas. These 7 patients were not included in calculating the results, because for only 1 (case 6) did we know the degree of relief obtained from cholecystectomy, and that patient did not live long enough before becoming ill again to allow confirmation of this.

## RESULTS

Thus, there were 83 patients alive at least five years after the operation about whom we had information. On the basis of these we have attempted to evaluate the results, bearing in mind the preoperative complaints and the relative degree of relief obtained (table 5). Percentages are based on these 83 patients plus the 1 who died after the operation.

TABLE 5.—*Results of Cholecystectomy*

Patients	Results									
	Good		Fair		Poor		Operative Mortality		Results Unknown	
	Num- ber	Per- cent- age	Num- ber	Per- cent- age	Num- ber	Per- cent- age	Num- ber	Per- cent- age	Dead	No In- forma- tion
Men.....	11	52.4	3	14.3	6	23.6	1	4.8	3	4
Women.....	35	55.6	15	23.8	13	20.6	0	0	4	9
Totals.....	46	54.8*	18	21.4*	19	22.6*	1	1.2*	7	13

\* Percentages based on 84 cases.

TABLE 6.—*Reported Results of Cholecystectomy for Noncalculous Chronic Cholecystitis*

Authors	Date	Patients	Results		
			Cured, Percentage	Improved, Percentage	No Relief, Percentage
Stanton.....	1932	90	74.5	....	....
Mackey.....	1934	149	29.2	29.2	36.2
Graham and Mackey.... (minimal lesions only)	1934	161 (57)	31.7 (19.3)	33.5 (33.6)	29.8 (36.8)
Pfeiffer.....	1936	43	72.0	....	....
Schafer.....	1936	98	74.0*	....	26.0
Brown.....	1936	275	39.6	31.1	25.0
Present study.....	1940	84	54.8	21.4	22.6

\* Includes cured and improved patients.

A comparison of the results with those obtained by others who have performed cholecystectomy for noncalculous chronic cholecystitis is shown in table 6. It can be definitely said that none of the preoperative or operative findings was of much value in determining the prognosis. Regardless of how long the patients had had symptoms, roughly half of them obtained good results from cholecystectomy, and approximately a quarter of them were no better after operation than before. Most investigators agree that if a history of biliary colic is present cholecystectomy usually will give good results.<sup>2a</sup> Judd<sup>2a</sup> reported failures in less than 9 per cent of cases in which there was a history of colic,

whereas for almost half of those (46.4 per cent) without a history of colic cholecystectomy failed to give good results. In the present study approximately 80 per cent of patients who had colic were cured or benefited, whereas 75 per cent of those without colic received some benefit. Symptoms other than pain are less likely to disappear than is pain itself.<sup>21</sup> A "typical story" of disease of the gallbladder was not indicative of any better prognosis than was a history of vague dyspepsia. Twenty-one per cent and 25 per cent, respectively, of patients with such histories were not benefited. Even a history of jaundice seemed to have but little importance in prognosis in the present study. In 84 per cent of patients with a history of jaundice the results were fair to satisfactory, whereas 74 per cent of those who gave no such history obtained similar results.

Cholecystectomy is reported to be a failure in approximately 40 per cent of patients with a neurosis.<sup>22</sup> In the present study, the results in

TABLE 7.—*Results of Cholecystectomy in Relation to Appendectomy*

Condition	Cases	Results					
		Good		Fair		Poor	
		Cases	Percentage	Cases	Percentage	Cases	Percentage
Previous appendectomy....	36	20	55.6	6	16.7	10	27.8
Appendectomy with cholecystectomy.....	36	21	58.3	7	19.4	8	22.2
Appendix not disturbed....	11	5	45.5	5	45.5	1	9.1
Totals.....	83	46	55.4	18	21.7	19	22.9

25 per cent of the neurotic patients were poor, whereas treatment of the more stable patients was considered a failure in 20 per cent. Whether the appendix was removed or not seems to have made little difference in the results (table 7). Even the cholecystogram gave little help in making a prognosis. Seventy-eight per cent of the patients with normal cholecystograms who gave other evidence (clinical) of biliary disease were wholly or partially relieved by cholecystectomy. All 5 patients with nonfunctioning gallbladders were cured after cholecystectomy. The presence or absence of adhesions made little difference in the success of the operation, as in approximately 80 per cent of each group some relief was obtained by operation. The results were approximately the same regardless of whether or not hepatitis was observed by the surgeon.

Although there was no evident gross pathologic lesion according to the defined conditions of this study, comparison of the microscopic

21. Graham, E. A., and Mackey, W. A.: A Consideration of the Stoneless Gallbladder, *J. A. M. A.* **103**:1497-1499 (Nov. 17) 1934.

observations with the operative results showed good results to be equally distributed between those with minimal and those with marked cellular infiltration. In approximately a quarter of each group treatment was a failure.

#### COMMENT

Several questions present themselves. What effect does the removal of an apparently normal gallbladder have on physiologic function? It has been proved that the gallbladder has the same general activities as the intestine, namely, absorption, secretion and motor activity; it also concentrates bile.<sup>22</sup> The functional significance of the gallbladder is proved by the fact that its removal is usually followed in a few weeks by dilatation of the extrahepatic biliary tract. This dilatation is dependent on an intact sphincter of Oddi and is less when the common bile duct is drained postoperatively.<sup>23</sup> In dogs, cholecystectomy is soon followed by paresis of the sphincter of Oddi, which later in most instances becomes sufficiently competent to cause the extrahepatic biliary ducts to become dilated.<sup>24</sup> Even hypertrophy of the sphincter of Oddi may develop.<sup>3b</sup> The concentrating ability of the gallbladder is evidenced by its ability to prevent the development of jaundice for many hours after obstruction of the common bile duct.<sup>23</sup> That the pathologic functionless gallbladder can be removed without harm does not mean that removal of a normal gallbladder, which has a pressure-regulating function, is equally harmless.<sup>25</sup> What constitutes chronic cholecystitis, either pathologically or clinically, is not actually known.<sup>2a</sup> Some observers place the condition on the borderline between functional and organic disease.<sup>26</sup> After cholecystectomy for noncalculous chronic cholecystitis as high as 40 to 45 per cent of patients have postoperative complaints of one kind or another (table 6).<sup>27</sup> Reasons for this probably include

22. Ivy, A. C.: The Physiology of the Gall-Bladder, *Physiol. Rev.* **14**:1-102 (Jan.) 1934.

23. Mann, F. C.: A Physiologic Consideration of the Gallbladder, *J. A. M. A.* **83**:829-832 (Sept. 13) 1924.

24. Judd, E. S.: Relation of the Liver and the Pancreas to Infection of the Gallbladder, *J. A. M. A.* **77**:197-201 (July 16) 1921. Mann, F. C.: The Functions of the Gallbladder, *Physiol. Rev.* **4**:251-273 (April) 1924

25. von Haberer, H.: Surgery of the Biliary Tract, *Internat. Abstr. Surg.* **50**:319-320, 1930; in *Surg., Gynec. & Obst.*, April 1930.

26. Mackey, W. A.: Cholecystitis Without Stone: An Investigation of Two Hundred and Sixty-Four Operated Cases from the Clinical, Radiological, and Pathological Aspects; an Attempt to Determine the Factors of Service in Estimating Prognosis, *Brit. J. Surg.* **22**:274-295 (Oct.) 1934.

27. Pfeiffer, D. B.: The Indications for Surgery in Gallbladder Disease, *Pennsylvania M. J.* **39**:489-493 (April) 1936. Shafer, L. E.: The Surgical Treatment of the Stoneless Gallbladder, *J. Iowa M. Soc.* **26**:243-246 (May) 1936. Stanton, E. MacD.: The Stoneless Gallbladder: A Study of Operative Cases, *Am. J. Surg.* **18**:246-250 (Nov.) 1932. Broders.<sup>19</sup> Graham and Mackey.<sup>21</sup> Mackey.<sup>26</sup>

errors in diagnosis, residual disease either in adjacent organs or in the extrahepatic system and visceromotor disturbances, such as dyskinesia.<sup>28</sup>

What is the cause of the symptoms in these patients if one considers the gallbladder normal, and how does removal of this organ relieve the patient of symptoms of cholecystic disease? Inconclusive evidence exists that very slight changes in the gallbladder cause symptoms,<sup>29</sup> although some believe that such microscopic changes may furnish a focus from which infection spreads to other organs.<sup>1b</sup> Many believe that gallbladder colic may be caused by a functional disturbance of motility termed biliary dyskinesia.<sup>28</sup> Pilocarpine can produce spasm of the sphincter of Oddi and contraction of the gallbladder, with resultant pain, which can be relieved by the administration of atropine or of magnesium sulfate.<sup>30</sup> Other possible causes of symptoms are so-called pancreatic apoplexy, with regurgitation of pancreatic juice into the gallbladder and resulting cholecystitis, and abnormally secreted bile that contains, possibly too much bile salts, thus producing cholecystitis.<sup>28a</sup> The relief following cholecystectomy, some feel, is due to the removal of a mass of infected tissue,<sup>15</sup> although it is not always easy to prove that the tissue is infected.<sup>30</sup>

Others believe that the benefit derived from operation is due to the removal of many nerves,<sup>31</sup> the breaking of lymphatic pathways and the severance of adhesions around the cystic duct.<sup>32</sup> The operation, furthermore, enforces rest in bed and causes the patient to be careful in convalescence. Just how large a part these factors play in the results, especially in the type of cases reported in this study, is difficult to ascertain. In those cases in which the condition is due to dyskinesia, relief following removal of a normally functioning gallbladder is possibly due to paresis of the sphincter secondary to the operation.<sup>33</sup> Instrumental dilation of the sphincter has been suggested as an aid, but

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28. (a) Weir, J. F., and Snell, A. M.: Symptoms That Persist After Cholecystectomy: Their Nature and Possible Significance, *J. A. M. A.* **105**:1093-1098 (Oct. 5) 1935. (b) Snell.<sup>2b</sup> (c) Ivy and Sandblom.<sup>3b</sup>

29. Muller.<sup>6</sup> Martin.<sup>12a</sup>

30. Andrews, E., and Henry, L. D.: Bacteriology of Normal and Diseased Gallbladder, *Arch. Int. Med.* **56**:1171-1188 (Dec.) 1935. Judd, E. S.; Mentzer, S. H., and Parkhill, E.: A Bacteriologic Study of Gall Bladders Removed at Operation, *Am. J. M. Sc.* **173**:16-23 (Jan.) 1927. Nickel, A. C., and Judd, E. S.: Cholecystitis: A Bacteriologic and Experimental Study of Three Hundred Surgically Resected Gallbladders, *Surg., Gynec. & Obst.* **50**:655-662 (April) 1930.

31. Womach, N. A.: Pathologic Changes in Chronic Cholecystitis and the Production of Symptoms, *Surgery* **4**:847-855 (Dec.) 1938.

32. Cole, W. H., and Rossiter, L. J.: Relationship of Lesions of the Cystic Duct to Gall-Bladder Disease, *Am. J. Digest. Dis.* **5**:576-586 (Nov.) 1938.

33. Wolfer, J. A.: Diseases of the Gallbladder and Biliary Ducts, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 7, pp. 139-224. Footnote 24.



it has been shown experimentally that scarring occurs after such dilation and that the subsequent size of the papilla is the same as before.<sup>34</sup> Hence, if the papilla is patent, no further dilation should be carried out. Probably the explanation of the relief obtained lies in a combination of all the aforementioned factors. But until it is known what causes the symptoms associated with grossly normal gallbladders, whether it be (1) lesions near the nerve endings, such as tension, inflammation or ischemia,<sup>31</sup> (2) "hepatitis," cholangitis, pancreatitis, biliary dyskinesia or pylorospasm induced by the distended gallbladder<sup>22</sup> or (3) general lowering of the threshold of sensibility, little real progress will be made in evaluating the factors responsible for cure of the condition.

How can one determine preoperatively which patients will be benefited by cholecystectomy? This study would seem to indicate the impossibility of making a definite, sure prognosis. The good results were slightly higher among patients with a history of colic and a clinical picture more or less typical of disease of the biliary tract. Most of the patients with abnormal cholecystograms were benefited, but this group formed too small a percentage to be of much significance. Possibly a medical program should be tried for these patients first, as Mason and Blackford have suggested, operation being reserved for those who do not respond to medical therapy.<sup>35</sup> Lahey<sup>36</sup> has expressed the belief that if the symptoms are unrelieved by medical management the gallbladder should be removed regardless of the findings. However, in the final analysis, most important in determining which patients to operate on seems to be that intangible yet definite factor, clinical judgment.<sup>11a</sup>

#### SUMMARY

A study of almost 2,000 cases in which cholecystectomy was performed, irrespective of why it was performed, revealed that in approximately 18 per cent of the gallbladders stones were not found and that in almost a third of these (5.75 per cent of the total) there were no gross pathologic lesions and the gallbladder could not be distinguished grossly from the normal. A macroscopically nonpathologic gallbladder may be found at operation even in the presence of a history typical of disease of the gallbladder with biliary colic, jaundice and tenderness in the right upper abdominal quadrant. Half of the patients with appar-

34. Branch, C. D.; Bailey, O. T., and Zollinger, R.: Consequences of Instrumental Dilatation of the Papilla of Vater: An Experimental Study, *Arch. Surg.* **38**:358-371 (Feb.) 1939.

35. Ivy, A. C., and Bergh, G. S.: The Applied Physiology of the Extrahepatic Biliary Tract, *J. A. M. A.* **103**:1500-1504 (Nov. 17) 1934. Mason, J. T., and Blackford, J. M.: The Conservative Treatment of Cholecystitis, *ibid.* **99**:891-895 (Sept. 10) 1932. Brown and Delkart.<sup>18</sup>

36. Lahey, cited by Muller.<sup>6</sup>

ently normal gallbladders gave a history typical of disease of the gallbladder; one third had typical biliary colics, and one third gave a history of jaundice. I have considered several possible explanations of these symptoms, although no new evidence is offered. Half of the patients showed evidence of nervous exhaustion or neurotic tendencies. Almost 90 per cent of the cholecystograms showed normally functioning gallbladders. There was no constant relation of the operative findings to any of the preoperative findings. No evidence was found to support the view that hepatitis as described at the time of operation is of any significance in relation either to preoperative findings or to prognosis.

Microscopically, all specimens showed varying degrees of lymphocytic infiltration, although there was no relation between the degree of infiltration and the preoperative findings, the operative findings or the prognosis. The results of cholecystectomy in this study were similar to those obtained by others in similar cases, and the good results were fewer than in those cases in which definite pathologic lesions or stones were present. Fifty-five per cent of the patients were cured; 21 per cent were improved, and 23 per cent obtained no relief. The operative mortality was 1 per cent. There is no way to predict either before or at operation which patients with macroscopically normal gallbladders will be relieved of their symptoms after cholecystectomy. Regardless of the way in which the cases are grouped, approximately 1 of 4 patients received no benefit from operation.

# EXPERIENCES WITH INTRAMEDULLARY TRACTOTOMY

## I. RELIEF OF FACIAL PAIN AND SUMMARY OF OPERATIVE RESULTS

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AND

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It has long been known from the study of pathologic conditions affecting the brain stem that there are an anatomic separation and a physiologic dissociation of the fibers of the trigeminal nerve immediately on their entry into the brain stem. The fibers conducting the modalities of pain and temperature turn downward and in company with the nucleus of the spinal tract of the fifth nerve run throughout the length of the medulla oblongata and into the upper cervical portion of the cord. During their course, they emerge from under cover of the restiform body and take a superficial position on the lateral surface of the medulla. In this situation they form a distinct elevation on the surface of the medulla—the tuberculum cinereum. In the closed portion of the medulla the tuberculum cinereum lies below the restiform body and above the olivary eminence. The fibers mediating touch sensation, on the other hand, turn upward at the point of entry into the brain stem, end in the main sensory nucleus of the trigeminal nerve and thence by the secondary neuron ascend to terminate in the sensory nucleus of the thalamus. This brief description, although it is oversimplified, of the intramedullary pathways of the trigeminal system will serve as an adequate anatomic outline to explain the basis for the procedure now known as intramedullary tractotomy.

In 1938 Sjöqvist,<sup>1</sup> of Stockholm, Sweden, on the basis of his studies on the organization of the central trigeminal system, proposed that section of the descending tract of the trigeminal nerve in the medulla could be used to relieve facial pain. An obvious theoretic advantage of this procedure was that touch sensation could be spared and that the face would not feel cold, stiff and numb as after section of the sensory root. A second advantage was the sparing of the motor com-

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From the Neurosurgical Service of the Hospital of the University of Pennsylvania.

1. Sjöqvist, O.: Eine neue Operationsmethode bei Trigemineuralgie: Durchschneidung des Tractus spinalis trigemini, *Zentralbl. f. Neurochir.* 2:274 1938.

ponent. A third was the elimination of neuromyolytic keratitis, since some sensation would be retained in the eye. He also expressed the belief that such a central interruption would prevent postoperative dysesthesias. In his monograph<sup>2</sup> published in the same year, he reported on the results in 9 patients in whom the descending tract of the trigeminal nerve was sectioned in the medulla oblongata. Though his results in terms of relief of pain were variable, largely because the operation was a new, untried and experimental procedure, he established without question that it is possible to render the face analgetic and to relieve facial pain without grossly disturbing the sensation of touch.

Since his report there have been several other publications on the surgical results and physiologic effects of intramedullary tractotomy.<sup>3</sup> Last year, in a preliminary report,<sup>4</sup> the results of 12 intramedullary tractotomies performed in this clinic were reviewed. There are now available in the literature the observations made in 37 cases. However, little or nothing has been published on the late effects of this operation concerning either the sensory status or the neurologic sequelae. According to Sjöqvist, there are neither early nor late neurologic disturbances following the operation with the exception of paralysis of the recurrent laryngeal nerve, observed in 3 cases and thought to be due to handling of the vagal nerves during the operation. However, in his case protocols he stated that in case 4 the patient complained of numbness in the opposite side of the body and that in case 9 the patient was more ataxic after the operation than before. In Rowbottom's case 3 the patient was said to have mild ataxia of the homolateral arm following operation. In a case reported by Smyth, in which operation was performed by Jackson, the patient had disturbances in gait and ataxia of the arm.

At the time of publication of the report of 12 cases observed in this clinic, there was especial interest in exploring the possibilities of the procedure for the relief of facial pain. Little attention, therefore, was paid to the neurologic disturbances witnessed in the 12 patients, for it was assumed that they were unimportant and would disappear. Further

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2. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve: A Contribution to the Surgical Treatment of Facial Pain, *Acta psychiat. et neurol.*, 1938, supp. 17, p. 1.

3. Rowbottom, G. F.: Treatment of Pain in the Face by Intramedullary Tractotomy, *Brit. M. J.* 2:1073, 1938. Jackson, H., and Ironside, R.: Left Trigeminal Pain Treated by Sjöqvist's Medullary Trigeminal Tractotomy, *Proc. Roy. Soc. Med.* 32:219, 1939. Walker, E. A.: Anatomy, Physiology and Surgical Considerations of the Spinal Tract of the Trigeminal Nerve, *J. Neurophysiol.* 2: 234, 1939. Smyth, G. F.: The Systemization and Central Connections of the Spinal Tract and Nucleus of the Trigeminal Nerve, *Brain* 62:41, 1939.

4. Grant, F. C.; Groff, R. A., and Lewy, F. H.: Section of the Descending Spinal Root of the Fifth Cranial Nerve, *Arch. Neurol. & Psychiat.* 43:498 (March) 1940.

experiences with additional cases and the opportunity to follow 15 cases over many months now permit us to evaluate the operation as a method of relief of facial pain and to describe the nature and estimate the importance of the adventitious side effects. From our experience we have concluded that certain modifications in the situation of the incision are necessary in order to avoid disturbing and sometimes permanent neurologic sequelae.

The details of the proposed modification and the anatomic reasons for it will be dealt with in a separate article. In this communication we shall deal with the immediate and late results of medullary tractotomy performed in 17 cases. In 6 of these the operation was done for major trigeminal neuralgia and in 11 for malignant disease about the head in which the presence of severe, intractable pain served as indication for operation.

#### SURGICAL TECHNIC AND ANATOMIC CONSIDERATIONS

A unilateral suboccipital craniectomy is performed, with removal of the posterior rim of the foramen magnum and the arch of the atlas. After the dura is opened, the arachnoid membrane of the cisterna magna is torn and the cerebrospinal fluid allowed to escape. The tonsil of the cerebellum is gently retracted until the lateral aspect of the medulla with the emerging roots of the lower cranial nerves is exposed and the fourth ventricle is visualized. According to Sjöqvist, the location of the incision is determined by identifying the lowermost vagal rootlet. At this point an incision is made into the lateral aspect of the medulla, beginning just dorsal to the rootlet and extending dorsally for 3.5 to 4 mm. The depth of the incision is 3 to 4 mm. This cut divides the descending tract of the trigeminal nerve in the tuberculum cinereum and theoretically, at least, avoids the important nuclei and tracts in this neighborhood.

Though we cannot for lack of space go into the anatomic details in this report, our experience has convinced us that this advocated level of incision is altogether too high and that it is difficult, if not impossible, to avoid injuring the restiform body or the lateral and/or main cuneate nucleus by an incision in this region. As evidence for this opinion we point to the cross-sectional illustration of the extent of the proposed incision that appears in Sjöqvist's monograph. In this figure the lower half of the restiform body is included in the transection. We feel certain that the predominant neurologic disturbances we encountered in the performance of this operation, following Sjöqvist's directions, were due largely to injury of the restiform body. In the last 3 cases we have used the obex of the fourth ventricle and the olive as the landmarks and have cut the tuberculum cinereum at a level 4 mm. below the obex and about 2 mm. below the olive. This site is 12 to 14 mm.

more caudal than that recommended by Sjöqvist. With this modification we have not observed permanent neurologic disturbances (fig. 1).

#### RESULTS OF OPERATION

In figures 2, 3 and 4 are summarized the data obtained from examinations of 17 patients in whom the bulbospinal tract of the trigeminal nerve was sectioned. In figure 2 are grouped the results in 6 cases of major trigeminal neuralgia, and in figures 3 and 4, the studies on the 11 cases of malignant disease about the head. In 6 cases in which operation was performed for trigeminal neuralgia we have been able to obtain repeated follow-up examinations over periods ranging from one to eleven months. In 5 cases of malignant disease treated by operation it has been possible to obtain follow-up sensory and neurologic

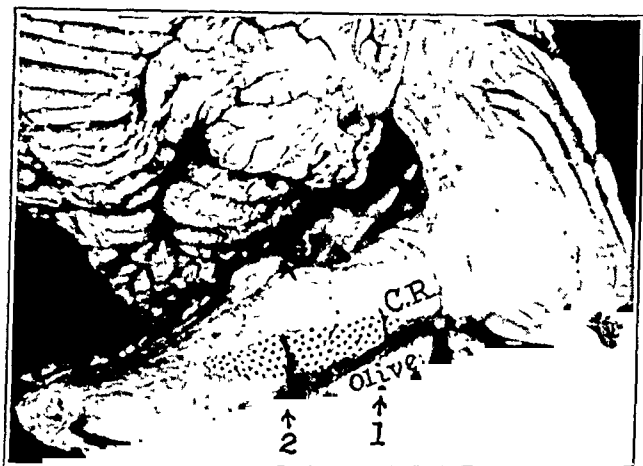


Fig. 1.—Prepared anatomic specimen, showing the surgical anatomy of the lateral aspect of the medulla. The stippled area outlines the tuberculum cinereum containing the descending tract of the trigeminal nerve. *X* indicates the obex of the fourth ventricle; *C.R.*, the corpus restiforme. The level of Sjöqvist's recommended incision is indicated by the line above the numeral 1. The more caudally placed level of the incision which we advocate is indicated by the line above the numeral 2. At the latter level the restiform body may be completely avoided and the descending tract is more superficial.

examinations as indicated in figure 3. These were obtained at intervals ranging from one to thirteen months after the operation. In 6 cases of malignant disease it has been possible to obtain a considerable number of neurologic and sensory data immediately after operation, but, either because of death or because the patients were too sick to come to the follow-up clinic, late postoperative studies could not be made. In 4 of these 6 cases, as is illustrated in figure 4, we have been able to secure through correspondence with the family some scanty and fragmentary data concerning the postoperative condition of the patients during the few months of survival. As is indicated on the illustrations,

the material will be treated in terms of immediate postoperative and late follow-up results, since experience has shown that there may be considerable alteration in both the sensory status and the neurologic disturbances in the months that follow operation.

*Immediate Sensory Results.*—In the upper row of sensory charts in figures 2, 3 and 4 is indicated the extent of sensory loss in the face immediately following operation. All patients were examined with graduated hairs and thorns and with hot and cold tubes. The sensory

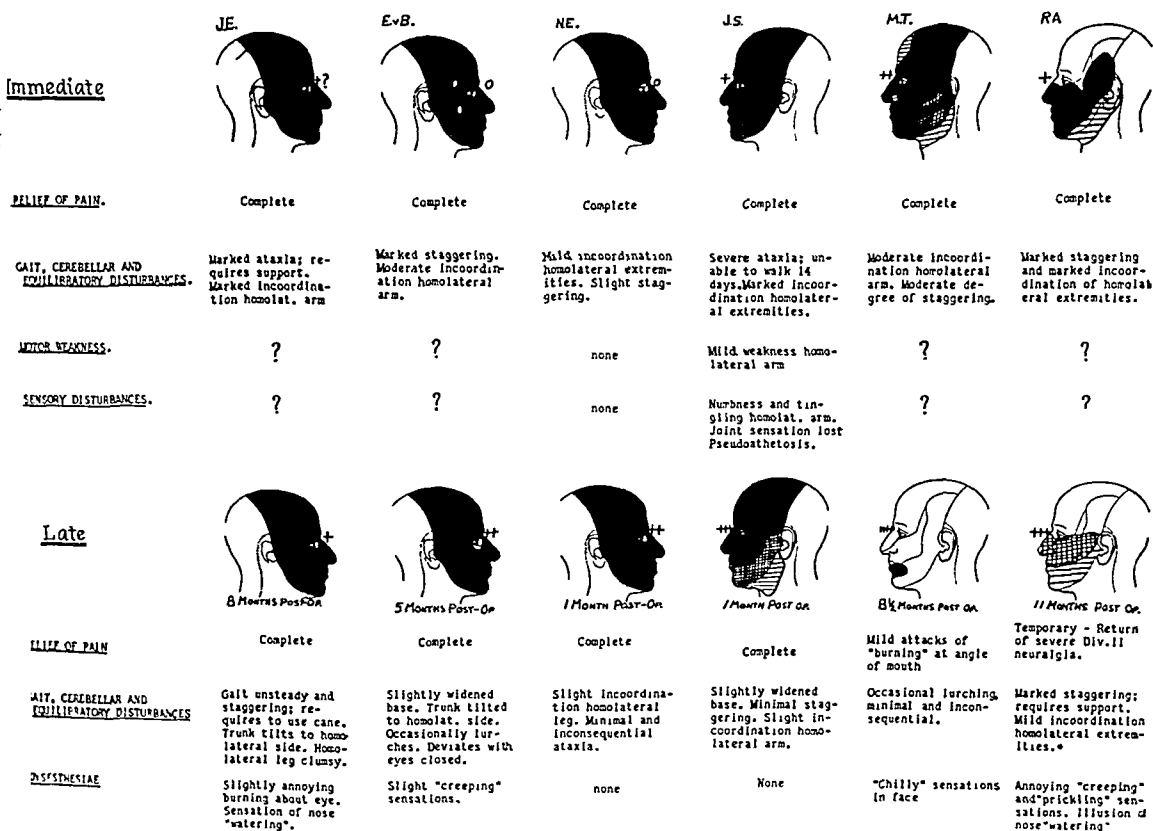


Fig. 2.—Tractotomy for major trigeminal neuralgia.

charts, however, deal only with the loss of pain sensation, since this is the important modality so far as the relief of pain is concerned. The solid black indicates complete analgesia, or the inability to feel as "sharp" a pressure of 40 Gm. or more with graduated thorns. The cross hatching indicates a marked hypalgesia, or the appreciation as "sharp" of 20 to 30 Gm. of pressure with graduated thorns. The linear shading indicates mild hypalgesia, or the appreciation as "sharp" of 10 Gm. or less of pressure with graduated thorns.

In 12 cases complete analgesia in the distribution of all three divisions of the trigeminal nerve immediately followed operation. In a few

instances, as is indicated on the sensory charts, there were small islands in which a few "pain points" could be found. In 2 cases (those of M. T., fig. 2 and W. S., fig. 3) there were curious combinations of analgesia and hypalgesia which did not conform to the conventional divisional territories of the face. In 1 case (that of R. A., fig. 2) the first division was entirely spared, with analgesia of the lower two divisions. In 1 case (that of C. K., fig. 3) the sensory result was unsatisfactory, there being only mild hypalgesia in all three divisions. In 1 case (that of

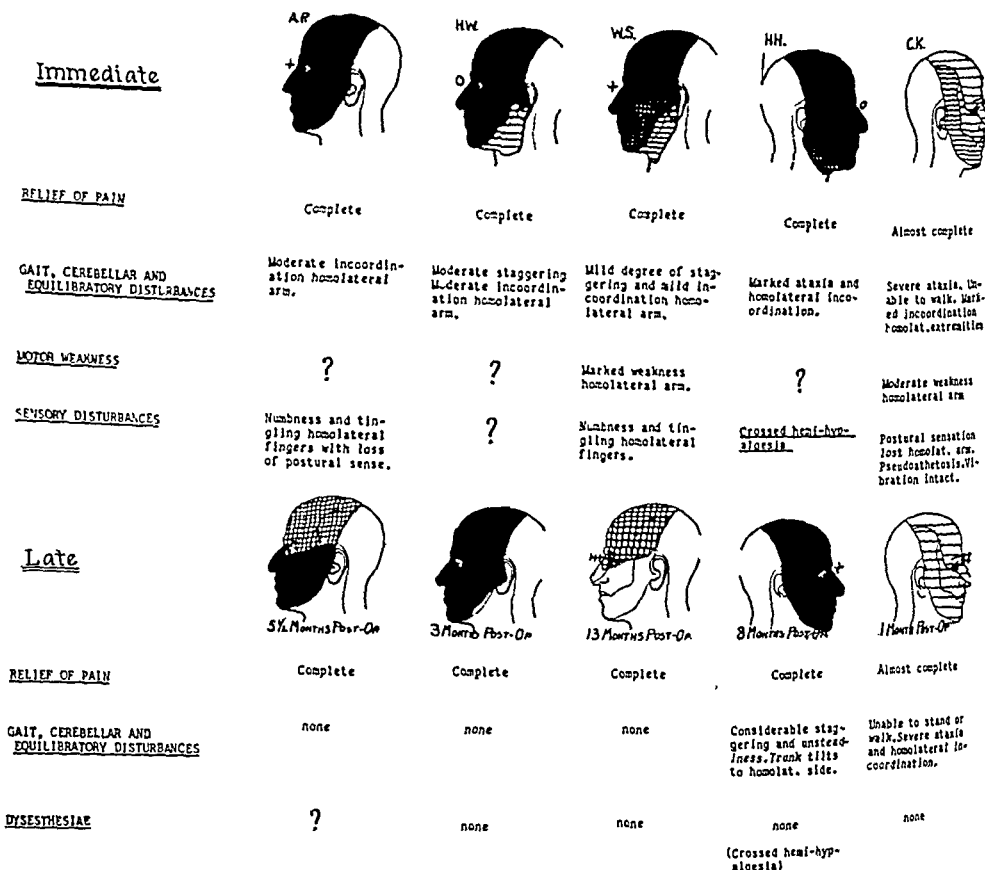


Fig. 3.—Tractotomy for malignant disease about the head.

F. W., fig. 4) the sensory loss could not be charted owing to a post-operative psychosis, but it was our impression that the impairment of sensation was slight.

On careful testing with graduated hairs, touch sensation was found to be slightly decreased in all instances in which analgesia existed, but this was difficult if not impossible to determine with ordinary cotton wool testing. The loss expressed itself as a diminution in the number of touch points per square centimeter, with or without a change in threshold.



The disturbances in temperature sensation were capricious and did not conform to the loss in pain sensibility. Sometimes with complete analgesia there was fairly good appreciation of temperature, and sometimes there was complete thermanesthesia. Occasionally heat would be appreciated but not cold, or vice versa. In an area of moderate hypalgesia, temperature might be well appreciated or, on the other hand, not at all. This agrees with the results of Spiller's<sup>5</sup> sensory studies, made many years ago in cases of thrombosis of the posterior inferior







	JK	EP	RJ	AMC	JG	FW
<u>Immediate</u>						
<u>RELIEF OF PAIN</u>	Complete	Complete	Complete	No pain complained of	No pain complained of	Questionable
<u>GAIT, CEREBELLAR AND EQUILIBRARY DISTURBANCES</u>	Moderate incoordination homolateral extremities	none	Marked ataxia; unable to walk. Marked incoordination homolateral extremities.	Late post-operative psychosis followed by pneumonia and death on 14th. day	Late post-operative pneumonia accompanied by psychosis. Death on 17th. day	Staggered badly and required support.
<u>MOTOR WEAKNESS</u>	?	none	Marked weakness in homolateral arm.	Pulmonary carcinoma found at necropsy	Pulmonary abscess found at necropsy	?
<u>SENSORY DISTURBANCES</u>	?	?	Loss of postural sense in fingers. Vibration intact. Dys-stereognosis			?
	?	?	?			?
<u>Late</u>						
	4 MONTHS Post-Op.	6½ MONTHS Post-Op.	2 MONTHS Post-Op.			1½ MONTHS Post-Op.
<u>RELIEF OF PAIN</u>	Complete	Incomplete	Incomplete			Apparently none (Psychotic)
<u>GAIT, CEREBELLAR AND EQUILIBRARY DISTURBANCES</u>	?	none	Considerable staggering and requires support to walk. Incoordination homolateral arm.			?
<u>HYESTHESIAE</u>	?	?	?			?

Fig. 4.—Further data on tractotomy for malignant disease about the head.

cerebellar artery, in which he found a noncorrespondence between the modalities of pain and of temperature.

It will be seen that on a number of sensory charts the disturbances in sensation extended for variable distances down the neck. This is due, as Lewy<sup>6</sup> pointed out, to the sensory overlap of the trigeminal field.

5. Spiller, W. G.: Remarks on the Central Representation of Sensation, *J. Nerv. & Ment. Dis.* 42:399, 1915.

6. Lewy, F. H.: The Role of Cervical Nerves in Facial Sensations and the Quantitative Disturbance of Sensitivity in Major Trigeminal Neuralgia, *Am. J. M. Sc.* 196:564, 1938.

*Immediate Relief of Pain.*—In 15 cases there was complete relief of pain following tractotomy. This included all cases of major trigeminal neuralgia. In 1 case (that of C. K., fig. 3) there was marked but not complete relief. In 1 case (that of F. W., fig. 4), in which there developed a postoperative psychosis, the result was questionable, but we feel that in this case the procedure was probably a failure. In both of these instances the sensory result was unsatisfactory.

*Immediate Neurologic Disturbances.*—In 14 of 15 cases in which it was possible to make postoperative neurologic examinations there were varying degrees of neurologic disturbance, ranging from very mild and transient to severe. The most evident disturbance in the early postoperative days was a wild incoordination of the homolateral arm, i. e., homolateral to the side of the medullary incision. The patient was usually unable to use the arm for feeding himself or for handling objects. The incoordination of the homolateral leg was far less. Nystagmus was present in a few instances. The static cerebellar disturbances tended to decrease and by the end of a week were slight in most cases. In several instances, however, incoordination of the arm persisted for a number of weeks. In spite of the absent or greatly diminished static cerebellar signs by the end of a week, the patient showed considerable disturbance in gait. This was, as has been stated, out of all proportion to the incoordination of the extremities that one was able to elicit while the patients were in bed. The disturbance in gait was characterized by standing with a widened base, staggering and falling to the homolateral side and a peculiar inclination of the upper part of the trunk to the homolateral side, reminiscent of the posture of a man leaning into a strong wind. By the end of two weeks these disturbances in gait had decreased or largely disappeared in most cases, but in several (those of J. E. and J. S., fig. 2, H. H. and C. K., fig. 3, and R. J. fig. 4) they persisted to the time of discharge.

In 4 cases there was weakness of the homolateral arm, which in 3 persisted past the time of discharge.

In 5 cases the patients complained of numbness and tingling in the homolateral hand and fingers, which again in 3 instances persisted until discharge. In 4 patients with this complaint who were carefully examined, loss or marked diminution of postural sensation was found in the fingers and wrists. A point of considerable interest was that vibratory sensation in these patients was intact.

#### LATE OBSERVATIONS AFTER TRACTOTOMY

*Late Sensory Status.*—In 11 cases in which late sensory examinations of the face were made one to thirteen months after operation, there were a number of alterations. Whereas in the immediate postoperative period 7 of the 11 patients who were followed showed complete analgesia of

the entire trigeminal field, late examination showed that 5 had analgesia in all three divisions. In 2 cases (those of J. S., fig. 2, and A. P., fig. 3) the analgesia had faded in the third and first divisions respectively. In 1 case (that of M. T., fig. 2) an original analgesia had almost entirely disappeared, leaving only a small patch of hypalgesia beneath the mouth. In another case (that of W. S., fig. 3), a profound degree of sensory loss in all three divisions of the face had faded to only a mild hypalgesia in the first division. About the same result was obtained in the case of R. A. (fig. 2), in which analgesia of the third and second divisions had largely disappeared, leaving moderate hypalgesia eleven months later.

It is obvious from the sensory studies on this material that the initial physiologic loss of sensation is not an exact measure of the fibers cut, nor is it possible to evaluate the sensory status until several months have passed. There is no doubt, however, that the degree and extent of loss of pain sensation is as great and as enduring with section of the bulbospinal tract as it is with section of the sensory root, provided the incision is made properly.

*Late Relief of Facial Pain.*—Of the 6 patients with major trigeminal neuralgia on whom operation was performed, 4 had when last seen, one to eight months after the operation, complete relief from neuralgic pains. One patient (M. T., fig. 2) complained of paroxysms of burning at the angle of the mouth, which were not distressing. However, because of the slight residual sensory loss in her face, it is possible that her neuralgia may return. One patient (R. A., fig. 2), the only patient with trigeminal neuralgia in whose case our treatment failed, had a return of severe neuralgia in the second division after relief lasting eleven months.

Of the 9 patients with malignant disease on whom tractotomy was performed and on whom we have follow-up data relating to relief of pain, 5 had complete relief one to thirteen months after the operation. Two patients (E. P. and R. J., fig. 4) had marked, though incomplete, relief. This was probably due to extension of their carcinoma to other regions of the head, outside the distribution of the sectioned trigeminal tract. Another patient (C. K., fig. 3) still had a mild degree of pain at the time of his death, one month after operation. This patient had from the time of operation an inadequate sensory loss. Another patient (F. W., fig. 4), in whom there was apparently no sensory loss produced by the operation, continued to have unabated pain, and the treatment, therefore, must be considered a failure.

*Subjective Facial Sensations.*—Information on the presence of subjective facial sensations was obtained only in our cases of trigeminal neuralgia. Four of the 6 patients admitted on questioning that they experienced various kinds of facial sensations although in no instance were these complained of spontaneously. However, 1 patient (J. E.

fig. 2) occasionally took acetylsalicylic acid because of a slightly annoying burning and "sore" sensation around his eye, and another (R. A., fig. 2) rubbed his face with liniment because of prickling and creeping sensations. Two patients stated that they had creeping sensations or a chilly feeling in the face. One patient who at the end of five months stated that he had no facial sensations and is thus listed as having none (E. V. B., fig. 2) recently wrote us stating that he feels a chilly sensation on the analgetic side of his face and that when rain strikes his face it has an icy feeling.

These results are not altogether surprising, since it is well known that in the presence of thrombosis of the posterior inferior cerebellar artery, with which the descending tract of the fifth nerve is invariably involved in the softening, dyesthesias of varying kind and intensity occur in the majority of cases.<sup>7</sup> There is no theoretic reason why unpleasant facial sensations should not occur as frequently after tract section as they do after root section. Nevertheless, none of our 15 patients have complained of severe or distressing facial sensations.

As a matter of fact, the patients are hardly aware that their faces feel any different on the analgetic side. Only when they run the hands over the face or during shaving do they notice that the sensation is somewhat less than on the intact side. In no case were there any complaints of numbness or of thick or frozen sensations, such as are experienced after section of the sensory root.

*Late Neurologic Disturbances.*—In 9 of 13 cases in which data are available there were varying degrees of neurologic disturbance at intervals of one to thirteen months after the operation. In 4 instances these disturbances were minor and academic. They consisted of occasional lurching, some difficulty in walking on stairs, slight veering of gait to the homolateral side, a little clumsiness with the homolateral leg in walking or a little difficulty in performing complicated tasks, such as typewriting. In 5 cases, however, the disturbances were more severe. There were 2 such cases among those in which operation was done for trigeminal neuralgia. One patient (J. E., fig. 2) required the use of a cane to venture out on the street, although he was able to get around his house easily. He stood with a widened base; he tended to stagger to the homolateral side, and his trunk was inclined to the side operated on. Another (R. A., fig. 2) eleven months after operation was unable to walk without support. This patient, however, had symptomatic trigeminal neuralgia engrafted on multiple sclerosis. Although he had had marked ataxia of both legs before operation and it is therefore difficult to appraise the effect of the operation on the neurologic picture, the fact remains that he was more ataxic after operation than before.

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7. Winther, R.: Tractotomy Viewed in the Light of the Pathology of the Medulla Oblongata, *Acta psychiat. et neurol.* 14:243, 1939.

Three patients operated on for malignant disease (H. H. and C. K., fig. 3, and R. J., fig. 4) had marked neurologic disturbances. C. K. and R. J. were unable to walk without support and had marked incoordination in the homolateral extremities at the time of their death, one and two months respectively after operation. Possibly, had they survived longer, much of their neurologic disability would have disappeared. H. H. was able to walk unsupported eight months after operation but staggered considerably. There were a widened base and an inclination of the trunk to the homolateral side. He also had hemihypalgesia of the opposite side of his body; this was the only instance in our series in which there was a Wallenberg syndrome produced by the operation. Four patients (E. P., fig. 4, and A. P., H. W. and W. S., fig. 3) were entirely free of neurologic disturbances six and one-half, five and one-half, three and thirteen months respectively after operation.

*Summary of Available Follow-Up Data in Fifteen Cases of Tractotomy One to Thirteen Months After Operation*

	Trigeminal Neuralgia 6 Cases	Malignant Disease 9 Cases	Not Known
Complete relief of pain.....	4	5	
Partial relief of pain.....	1	3	..
No relief of pain.....	1	1	
Satisfactory facial analgesia.....	4	3	} 4
Inadequate facial analgesia.....	2	2	
Marked neurologic disturbances.....	1*	2	} 2
Moderate neurologic disturbances.....	1	1	
Minor neurologic disturbances.....	4	..	
No neurologic disturbances.....	..	4	
Subjective facial sensations.....	3	..	} 5
No subjective facial sensations.....	3	4	

\* Underlying diffuse degenerative diseases of central nervous system.

*Morbidity and Mortality.*—There were 2 deaths in our series of 17 patients, both due to the late development of pneumonia. Both patients were examined at autopsy. One had extensive pulmonary carcinomatosis and 1 multiple pulmonary abscesses. At the time they were operated on it was felt that they would probably survive for six months, and it was thought, therefore, that an attempt to relieve them of their intractable pain was justified.

The periods of hospitalization ranged between eight and twenty-one days, with an average stay of fourteen days.

Brief mention may be made of two complications, neither of which, however, was serious. In most instances the patients complained of severe headache for one to three days, probably due to loss of cerebrospinal fluid, blood in the posterior fossa and air in the subarachnoid space. Four patients had intractable hiccups, usually appearing on the second to the fifth day and lasting three to nine days. All medica-

tion was unavailing, although temporary relief was afforded by inhalation of carbon dioxide.

#### COMMENT

A summary of the late results obtained in the series of 17 cases of tractotomy is found in the accompanying table. The neurologic sequelae of tractotomy as described here might seem to preclude its use. However, the suggested shift in the position of the incision into the medulla has enabled us to relieve the pain in the last 3 cases of trigeminal neuralgia with few and minor resulting disabilities. If further experience indicates that the asynergic and dysmetric complications can be reduced to this extent, a definite place exists for this procedure.

Not infrequently patients are encountered who complain of a burning sensation in the face between the paroxysms of major neuralgia. Our experience has been that frequently after relief of pain by root section this burning sensation continues as a dysesthesia in the anesthetic area. For such patients tractotomy may be particularly indicated, because the absence of subjective sensory change in the face following this procedure as compared to the total anesthesia accompanying root section may go far to prevent aggravation of the burning dysesthesia. And this persistent dysesthesia is a very distressing sequela to root section.

If a patient has trigeminal neuralgia in all three divisions, tractotomy should be considered, because the corneal reflex is spared and keratitis avoided. In the rare instances in which the neuralgia has recurred on the opposite side of the face, the initial pain having been cured by complete sensory and motor root section, the recurring pain can be relieved by tractotomy without any possibility of damage to the remaining motor root. When a cancer of the mouth, the base of the tongue or the mandible is present, requiring a suboccipital craniotomy for section of the fifth, ninth and posterior cervical roots for relief of pain, tractotomy is easier to perform than transection of the trigeminal root at the pons.

Under these limited conditions, therefore, a very real place for medullary tractotomy may be found in the treatment of trigeminal neuralgia. Because of the potential neurologic sequelae following a badly placed incision into the medulla, this procedure will never be used routinely even by those experienced with it. But every neurosurgeon dealing with many patients with trigeminal neuralgia should know how to perform this maneuver whenever the proper indication for its use exists.

# FUNCTIONS OF THE EXTRAHEPATIC BILE DUCTS AND SECRETORY FUNCTION OF THE LIVER

## IV. CLINICAL STUDY ON THE RELATION BETWEEN THE DUODENAL MOVEMENTS AND THE EVACUATION OF BILE INTO THE DUODENUM DURING FASTING

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Ganter<sup>1</sup> observed the movements of the duodenum in man by the use of the balloon method. Weitz and Vollers,<sup>2</sup> Peiper and Isbert,<sup>3</sup> Konishi<sup>4</sup> and others have conducted studies by the same method. Studies on the flow of bile into the duodenum during fasting have been made by numerous investigators since Einhorn devised the duodenal drainage method. Lyon<sup>5</sup> reported that during fasting the bile normally is not seen in the duodenal drainage fluid and when seen indicates a pathologic condition in the biliary tract. Inoue<sup>6</sup> observed in his studies that the bile was generally expelled continuously and rarely in a periodic manner. Iwanaga<sup>7</sup> reported that in man the bile was seen in the duodenal drainage fluid, while experiments on dogs (duodenal fistula) showed that generally an outflow of bile did not occur during fasting and occurred rarely in the so-called "periodic outflow" for two to seven minutes at intervals of one to two hours. He assumed that these differences observed in man and animals were probably due to the mechanical stimulus of the duodenal drainage.

In order to study simultaneously the relation between the movements of the duodenum and the discharge of bile in man during fasting, we devised a method by which we have been able to obtain excellent

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1. Ganter, G.: *Arch. f. d. ges. Physiol.* **201**:101, 1923.
2. Weitz and Vollers, W.: *Ztschr. f. d. ges. exper. Med.* **52**:723 and 747, 1926.
3. Peiper, A., and Isbert, H.: *Jahrb. f. Kinderh.* **119**:291, 1928; **120**:48, 306 and 312, 1928; **122**:263, 1928.
4. Konishi: *Jap. J. Exper. Gastroenterol.* **11**:144, 1936.
5. Lyon, B. B. V.: *Diagnosis and Treatment of Disease of Gallbladder and Biliary Ducts*, J. A. M. A. **73**:980 (Sept. 27) 1919.
6. Inoue: *Kyotogaku Zasshi M. J.*, 1923, vol. 20, nos. 1, 2, 3, 4, 9 and 10.
7. Iwanaga, H.: *J. Jap. S. A.* **25**:1004, 1924.

and often conclusive results. The method is as follows (fig. 1): A drainage tube about 100 cm. long, made up of an outer and an inner tube, was used. A balloon (7 to 8 cm. in length) was connected to the tube, together with a metallic olive. The duodenal tube was marked at points 60 and 75 cm. from the metallic olive. The outer tube was used for inflating the balloon, while the duodenal fluid flowed out through the inner tube. In figure 1, *A* is the outlet from which the duodenal fluid dripped. The amount was measured by kymographic recording of the fall of the drops. Further, the amount which fell during periods of five to ten minutes was measured, and quantitative determination of

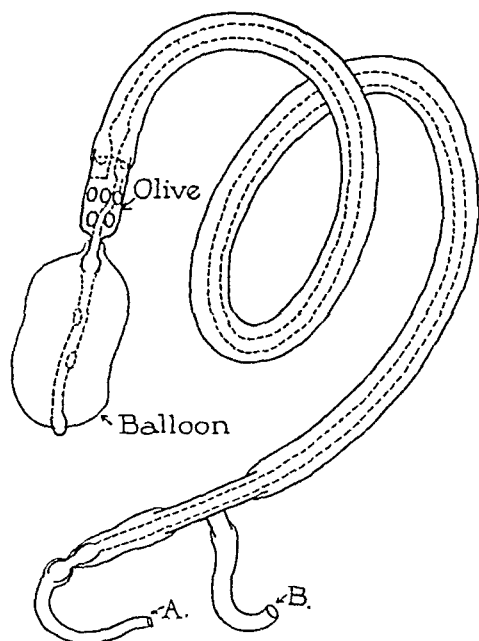


Fig. 1.—Apparatus used. See text for description.

the concentration of bile pigment (Meulengracht's method) was carried out. In the same figure, *B* leads out from the balloon in the duodenal cavity and is connected with the tambour, making it possible to record the movements simultaneously with the measuring of the drops of duodenal fluid.

A brief outline is given of the results obtained. The subjects were given a light meal on the night before investigation, and no food was given in the morning. The observations began at 9 a. m.

#### PERIODIC TYPES OF ACTIVITY

CASE 1 (third observation, Oct. 10, 1935).—The subject was a man aged 44. As may be seen in figures 2 and 3, this subject showed typical periodic activity in both the duodenal movement and the outflow of bile. In curve 1, for the resting



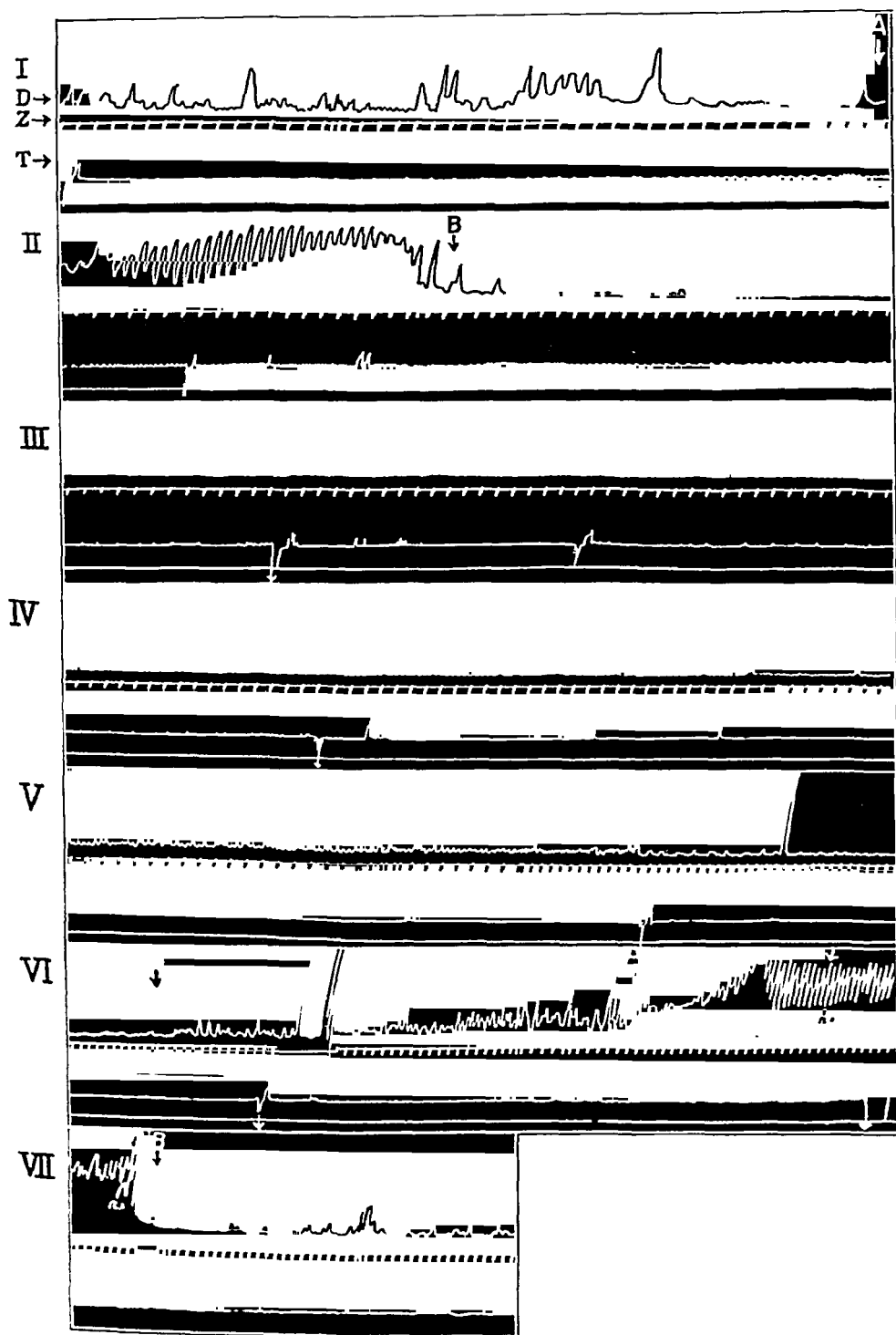


Fig. 2.—I, II, III, IV, V, VI and VII are connecting. *D*, duodenal movement; *Z*, time (ten seconds); *T*, drops of duodenal fluid.

period, that is, from *B* to *C*, the duodenum was almost inactive and only slight waves of respiration were seen. The active period, that is, from the start of the curve to *A* and from *C* to *A'*, showed that at the beginning short waves of 2 to 3 cm. in groups of two to three waves occurred at intervals; then the height of the waves and the grouping of the waves gradually increased, so that the resting intervals were shortened. In this period the resting and active movements occurred intermittently, so that it may be also said to be the intermittent active period. The period of tetanic movement is the period from *A* to *B* and from *A'* to *B'*

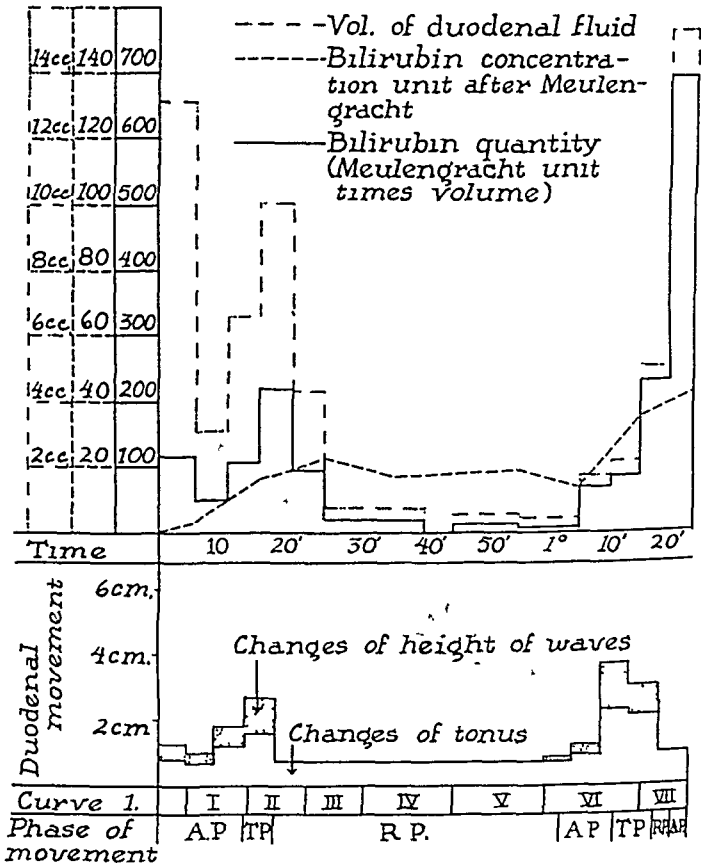


Fig. 3—Duodenal movements and discharge of bile in case 1

During this the levels of tonus rose suddenly and strong peristaltic waves numbering about thirty to sixty occurred continuously. The tetanic movement ceased suddenly and passed into the resting phase. With regard to the flow of bile into the duodenum, as may be seen in figures 2 and 3, the quantity of bile increased gradually up to the beginning of the tetanic period. When the duodenal movements passed from the tetanic to the resting phase, the quantity of bile decreased suddenly and the drops of duodenal liquid almost ceased. After the resting period, with the duodenal movements again active, the outflow of bile also increased. In this case, almost the same results were obtained on the second (October 3) and the fourth (October 21) observations, but the first observation did not show the periodic type of activity

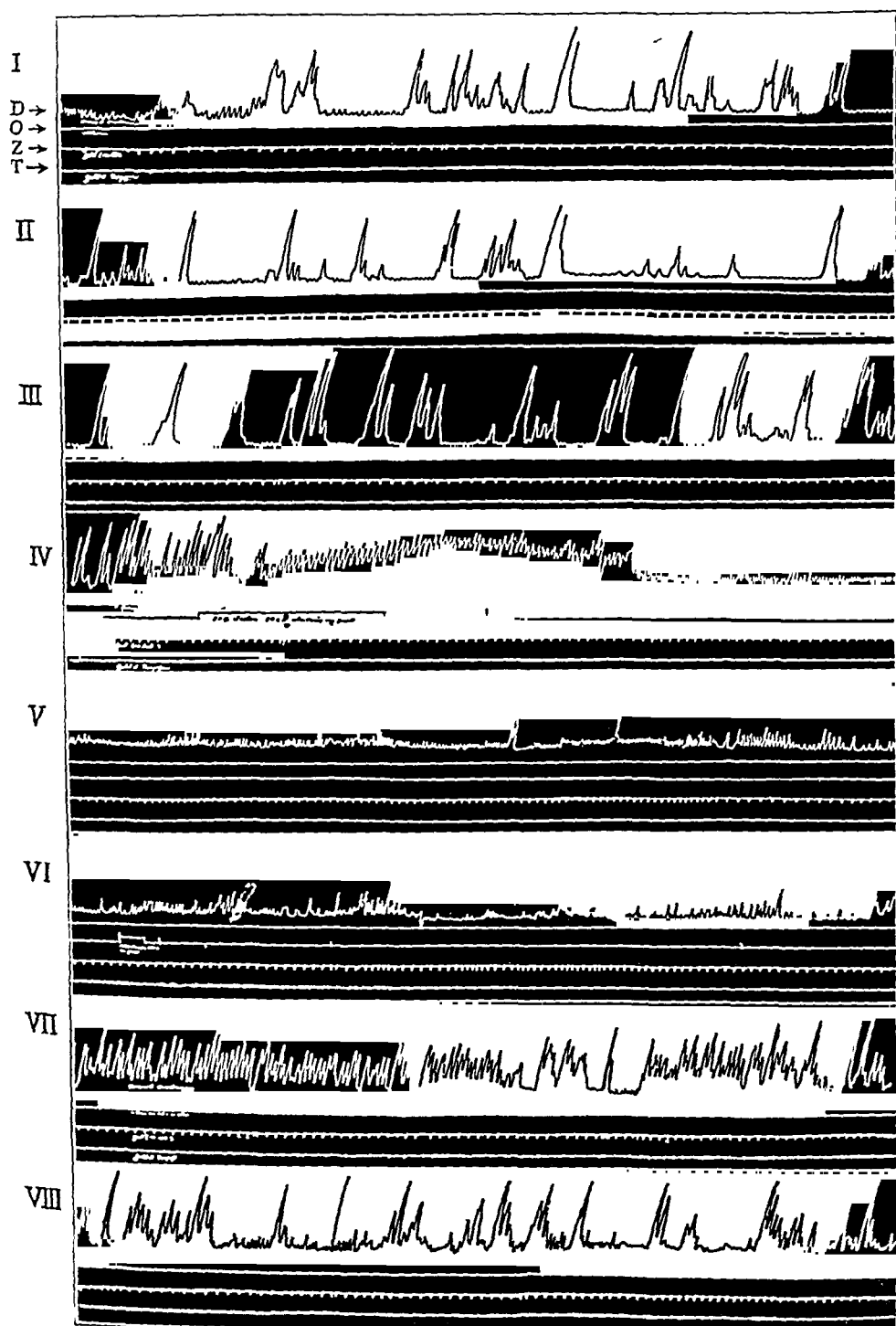


Fig. 4.—I, II, III, IV, V, VI, VII and VIII are connecting. *D*, duodenal movement; *O*, zero pressure line; *Z*, time (ten seconds); *T*, drops of duodenal fluid.

CASE 2 (Aug. 13, 1935).—The subject was a man aged 44. As may be seen in figure 4, the duodenal activity showed periodic movements. The active phase lasted forty-five minutes; then the tetanic phase set in and continued for eight minutes, followed by a resting period of forty minutes, with a return to the active phase. With regard to the outflow of bile, the volume of duodenal drainage and the bilirubin content and its concentration gradually increased parallel from the

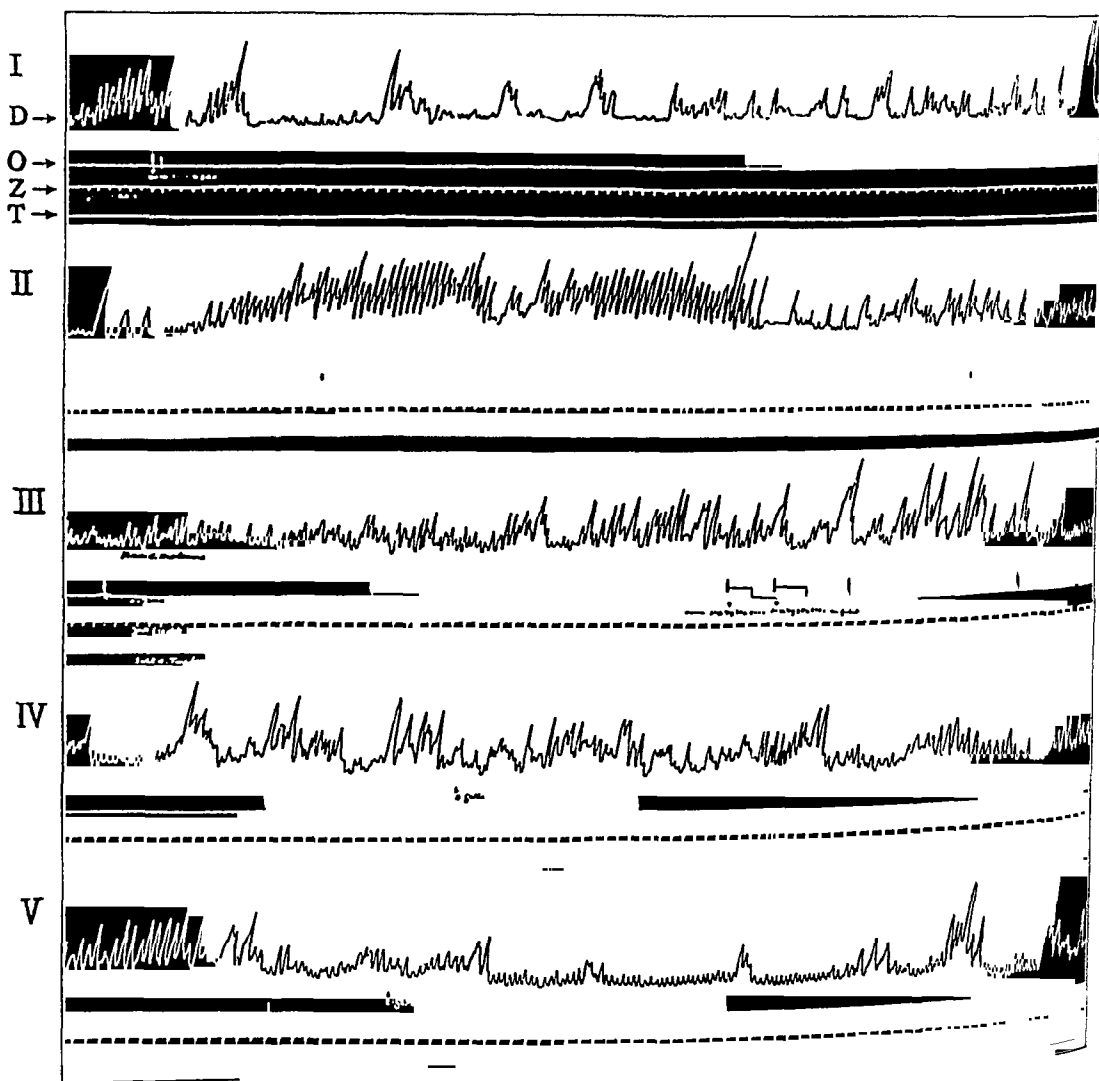


Fig. 5.—I, II, III, IV and V are connecting. D, duodenal movement; O, zero pressure; Z, time (ten seconds).

beginning until the middle of the tetanic period, according to the increased duodenal movements. The flow of bile ceased suddenly at the end of the tetanic period and also during the resting period. Duodenal movements occurred again twice; the fluid also flowed again, and its quantity and the concentration of bile increased gradually.

In 4 other cases almost the same results were obtained.

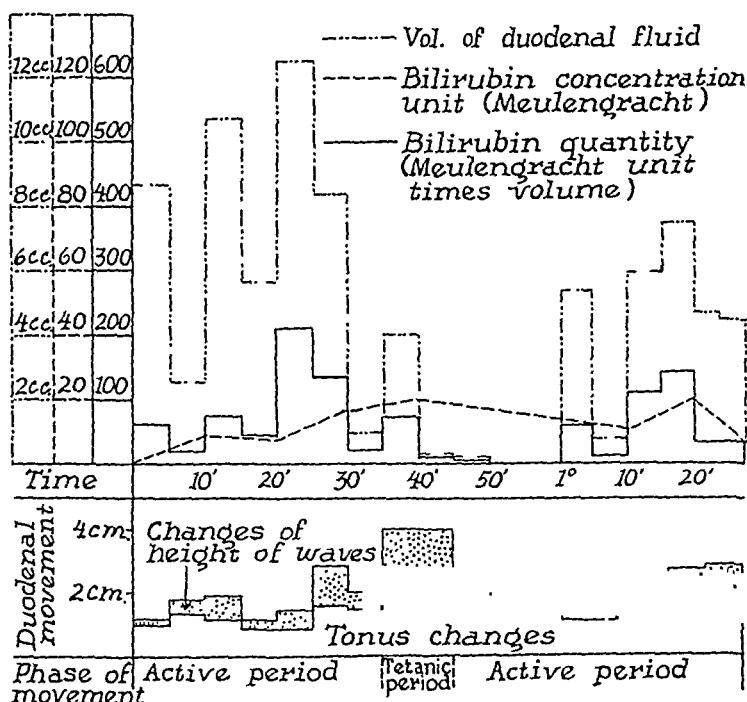


Fig. 6.—Duodenal movements and discharge of bile in case 7.

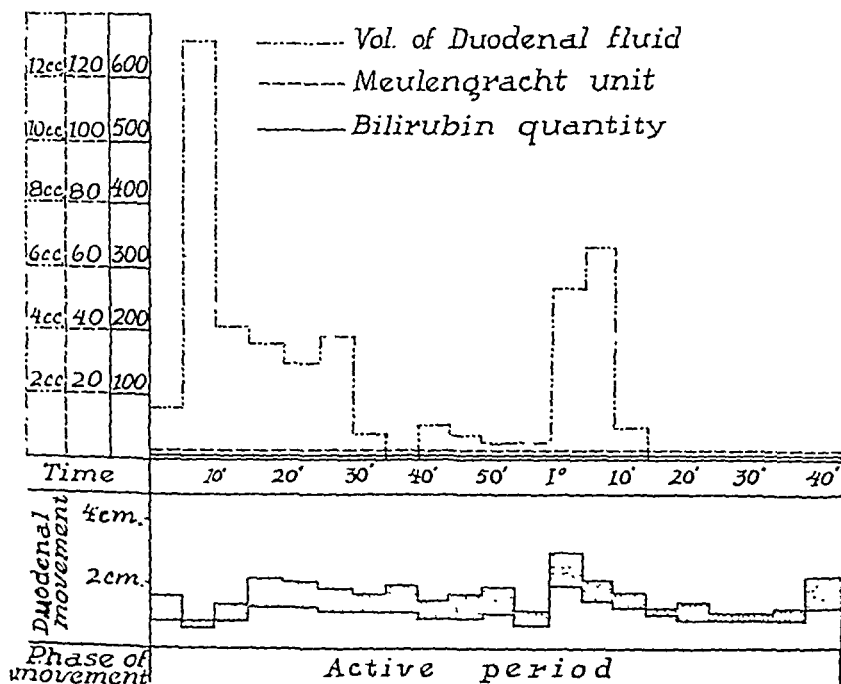


Fig. 7.—Duodenal movements and discharge of bile in case 11.

## NONPERIODIC TYPES OF ACTIVITY

CASE 1 (same subject as shown in figure 2; first observation, Sept. 20, 1935).—In this case, in the second, third and fourth observations periodic activity was observed, but on a different day, although under the same conditions, a nonperiodic type of activity was observed. As may be seen in figure 5, from the beginning the duodenal movement gradually became active, and after twenty minutes the tetanic movements occurred, but with the passing of the tetanic phase the resting phase did not appear and the movement continued to be active. With regard to the outflow of bile, a gradual increase from the start was seen, both in volume and in quantity of pigment; then a decrease occurred for the tetanic period, followed by another increase during the periods of duodenal activity.

CASE 7 (Feb. 28, 1936).—The subject was a man aged 28. The quantity of bile and its concentration increased gradually with the increase in duodenal activity (fig. 6). When the tetanic movement appeared, the bile outflow diminished; then it increased again with the next period of activity.

Investigations in 3 other cases (cases 8, 9 and 10) showed almost the same results as did the first observation in cases 1 and 7.

## ABNORMAL TYPES OF ACTIVITY

CASE 11 (Sept. 16, 1935).—The subject was a man aged 48. The duodenal movement was continuous (fig. 7), and there were no resting periods, as was also noted with the nonperiodic types of activity. But the duodenal fluid on examination showed no bile pigment throughout the period of investigation. Drainage was tried repeatedly, but only a cloudy fluid was obtained and no bile was observed. Cholecystographic examination was carried out and showed an abnormally large shadow of the gallbladder. After administration of two egg yolks the gallbladder contracted. In this case we assumed that the hypertonic function at the distal end of the choledochus had checked the evacuation of bile into the duodenum during the period of fasting.

## COMMENT

The investigations were carried out 14 times on 11 subjects, all in normal health. In 8 investigations in 6 cases a periodic relation between the duodenal movement and the outflow of bile was observed. In 5 cases there were nonperiodic types of activity, that is, the duodenum moved continuously, with intermittent flow of bile, and in 1 case no bile pigment was found in the duodenal drainage despite the continued movement of the duodenum.

Lyon asserted that under normal conditions bile should not be observed in the duodenal drainage fluid during fasting and that, when observed, it indicates a pathologic condition of the biliary tract. In our examinations, however, bile was observed in 10 of 11 cases. In the 1 case in which bile was not observed in the duodenal fluid and the unusual size of the gallbladder was ascertained by cholecystographic examination, the gallbladder was seen to decrease remarkably in size after digestion of two egg yolks. This fact seems to indicate that the gallbladder was in a dilated condition due to the stagnation of bile. Moreover, from our experimental studies on the mechanism of bile

evacuation (to be published later) it has been ascertained that when there was no evacuation of bile into the duodenum during fasting the resistance at the distal end of the common bile duct showed over 300 mm. of water pressure, so that despite the continued contractions the gall-bladder was not able to contract over the resistance pressure, and therefore the bile could not evacuate into the duodenum. From these facts we believe that when no bile is observed in the duodenal fluid during fasting an abnormally stagnant condition of the biliary tract is indicated.

Details regarding the relation between the periodic movements of the duodenum and the outflow of bile are shown in the accompanying table. The period of activity varied from eight to sixty-three minutes; the tetanic period, from three to eleven minutes, and the resting period, from three to forty-five minutes. The periods were never constant

*Relation Between Periodic Duodenal Movements and Outflow of Bile*

Case	Subject's Age	Date	Active Period, Minutes	Tetanic Period, Minutes	Resting Period, Minutes
1	49	Oct. 3, 1935	Over 10 38	3 11	23 9
1	49	Oct. 10, 1935	Over 13 8	5 7	45 3
1	49	Oct. 21, 1935	Over 30	11	34
2	44	Aug. 13, 1935	Over 46 63	7	Over 14
3	34	July 1, 1935	Over 33	7	Over 20
4	38	July 16, 1935	Over 27	7	Over 17
5	54	May 21, 1935	Over 60	7	Over 15
6	50	May 20, 1935	Over 50	5	Over 5

and varied greatly even with the same subject. Especially in case 1, on October 10, the first resting period was forty-five minutes, while the second was only three minutes. The subject in this case showed also a type of movement intermediate between the periodic and the nonperiodic. On October 3 and 21 periodic types of movement were seen, while on September 20 a typical nonperiodic type was seen. The same thing can be noted in the active and in the tetanic period.

With regard to the periodic outflow of bile into the duodenum. Inoue<sup>6</sup> observed that outflow of bile pigment in the duodenal drainage was generally continuous and rarely periodic. Iwanaga<sup>8</sup> observed the same fact and assumed that it was due to the stimulus of the duodenal drainage tube. In our examinations, however, bile pigment normally appeared both periodically and continuously, even as the movements of the duodenum are both periodic and continuous. These two types are not essentially be distinguished, and a number of intermediate types

8. Iwanaga, H.: *Central Org. Jap. M. Sc.* 20:883, 970, 1056, 1935.

are to be noted in the same subject examined under uniform physiologic conditions. Further details of these investigations will be given in our next paper.

With regard to the relation of the outflow of bile and the duodenal movements, it was noted that when the duodenum moved periodically during fasting the evacuation of bile was also periodic and that, while a flow of bile was seen during the active and the tetanic period, it ceased during the resting period. When the duodenum moved continuously, the evacuation of bile was also continuous, but rarely was any bile pigment observed.

#### CONCLUSIONS

1. During fasting the movement of the duodenum is periodic or nonperiodic. In the former there are three phases, active, tetanic and resting, repeated regularly. In the latter the movement of the duodenum is continuous, changing from the active to the tetanic phase, with no resting phase.

2. The outflow of bile during fasting was seen only during periods of activity of the duodenum; when the duodenal movement was periodic, the outflow of bile was also observed to be periodic, no bile flow being observed during the resting period. When the duodenal movement was continuous the outflow of bile was irregular but almost continuous.

3. In regard to periodic and nonperiodic movements, it is difficult to distinguish them essentially, and each shows varied changes due to numerous physiologic factors, so that it cannot be readily said which is normal and which is abnormal.

4. When no bile is observed in the duodenal drainage fluid despite continued movement of the duodenum during fasting, it may be assumed from this fact that a pathologic condition exists in the biliary tract. The resistance at the lower end of the common duct is high; that is, "hypertonic dyskinesia" of the biliary tract is indicated unless a complete obstruction of the biliary tract is observed.



# FUNCTIONS OF THE EXTRAHEPATIC BILE DUCTS AND SECRETORY FUNCTION OF THE LIVER

## V. EXPERIMENTAL STUDY ON THE RELATION BETWEEN THE MOVEMENTS OF THE DUODENUM AND THE FUNCTIONS OF THE BILIARY TRACT DURING FASTING

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The results of a study of the relation between the duodenal movements and the evacuation of bile into the duodenum in man during fasting have been given in a previous paper. However, in order that the present experimental work may be seen in proper correlation with the previous investigations, a brief outline of the latter will be given. It was found that when the movement of the duodenum was periodic the evacuation of bile was also periodic and that the evacuation occurred only during the active and tetanic periods of duodenal movement and was not seen during the resting period. When the duodenum moved continuously, bile was found in the duodenal drainage in all cases except 1, in which no bile pigment was found, although the duodenum continued active. This brings up the question: What mechanism causes the bile to evacuate periodically and nonperiodically only during the active periods of duodenal movement and to cease during the resting periods? Also, what is the explanation when no bile is seen in the duodenal fluid even though the duodenal movements are continuous? Concerning these phenomena, Boldyreff<sup>1</sup> stated the belief that during the period of activity of the stomach and the other digestive organs there should be contraction of the gallbladder causing evacuation of bile. Hosono<sup>2</sup> confirmed Boldyreff's opinion and explained that at the end of the resting phase of the stomach and the beginning of the active phase the gallbladder contracts and the sphincter of Oddi relaxes. However, several defects may be seen in the experiments carried out by these workers, and the phenomena of biliary functions cannot be fully explained by experiments on the obvious mechanisms.

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1. Boldyreff, W. N.: *Ergebn. d. Physiol.* **29**:485, 1929.

2. Hosono, S.: *Jap. J. Exper. Gastroenterol.* **7**:127, 148, 171, 189 and 212, 1932.

In this paper we wish to give the results obtained in our investigations on the evacuation of bile, the contraction of the gallbladder, the resistance of the sphincter of Oddi and the duodenal movements in fasting unanesthetized intubated dogs, with the observations made almost simultaneously. The methods used in our work have been given in a previous paper and will be only briefly given here. Double intubation of the common duct was carried out without injury to the gallbladder, and at the same time a duodenal fistula was made or a small balloon was placed inside the duodenal wall opposite the papilla of Vater. In figures 1, 2 and 3 are shown the apparatus used. By the use of the apparatus shown in figure 1 the changes in intracholedochal pressure, the flow of bile into the duodenum and the movements of the duodenum were recorded. With the apparatus shown in figures 2

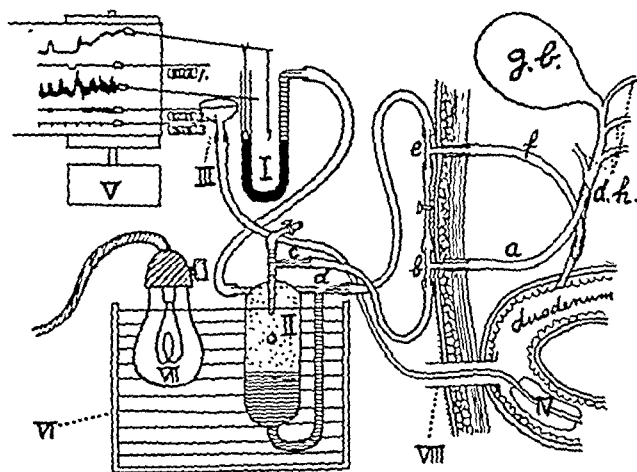


Fig. 1.—The following designations are used: *g. b.*, gallbladder; *d. h.*, ductus hepaticus; *ab* and *fc*, intubated cannulas; *I*, mercury manometer; *II*, drop counter of bile; *III*, tambour; *IV*, rubber balloon in the duodenum; *V*, kymograph; *VIII*, duodenal fistula.

When the tubing between *c* and *b* is disconnected by a clamp, the bile from the upper part of the biliary tract (*g. b.* and *d. h.*), passing through *a*, *b*, *c*, *II*, *d*, *e* and *f*, is evacuated into the duodenum. The volume and time of evacuation of bile are measured by a drop counter (*II*) containing liquid paraffin. The intra-choledochal pressure is traced with the U-shaped mercury manometer (*I*). The movements of the duodenum are traced by the tambour by air conduction from the duodenal balloon.

and 3 recordings of the changes in sphincteric resistance at the lower end of the common bile duct were added to the records.

#### PERIODIC TYPES OF ACTIVITY

CASE 1.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 12 Kg. The observation was made on the eleventh day after operation, March 6, 1936. The experimental method is shown in figure 1. As

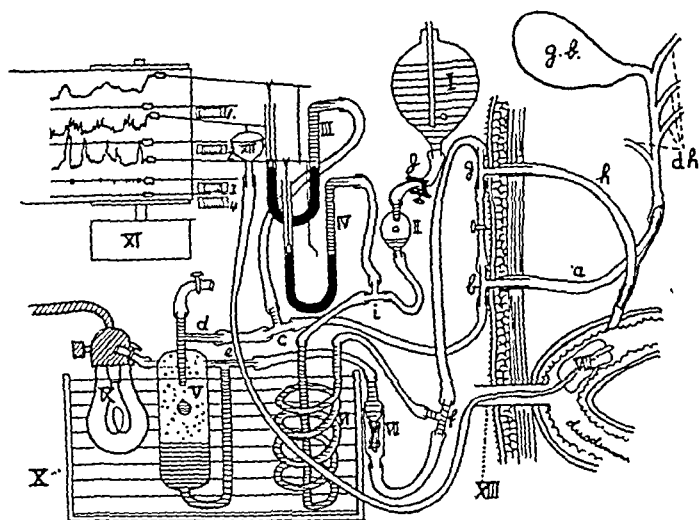


Fig. 2.—The following designations are used: *I*, flask containing Ringer's solution; *II*, drop regulator; *III* and *IV*, mercury manometers; *VI*, spiral glass tube; *VII*, William's valve, which prevents regurgitation of fluid.

In this, additions for the observation of pressure changes of the sphincteric mechanism are made to the apparatus in figure 1. The flask containing Ringer's solution is fixed at a height of 60 cm. or more, and the solution flows at a constant rate, passing through *II*, *i*, *VI*, *f*, *g*, *h* and the lower part of the choledochus into the duodenum. Therefore, when the pressure changes in this conduction system below *j* are traced by a manometer (*IV*), this would directly indicate the changes in tonus of the lower part of the choledochus. Regurgitation of Ringer's solution in the bile drop counter is prevented by a William's valve, so that when the pressure in the upper part of the duct overcomes the tonus of the sphincter of Oddi, the bile may be evacuated into the duodenum.

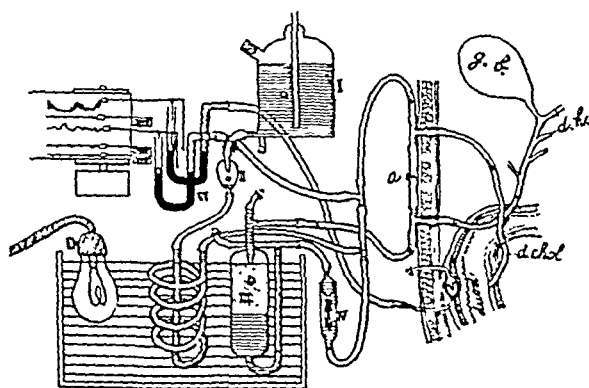


Fig. 3.—With this apparatus the movement of the duodenum was observed by a method in which a small balloon (*V*) was placed inside the duodenal wall. Otherwise this is the same as figure 2.

may be seen in figure 4, the duodenum showed periodic movements, and the curve is almost the same as that observed for man. During the resting phase of the duodenum the gallbladder continued to be relaxed and the intracholedochal pressure was only about 30 mm. of water, so that no bile was evacuated into the duodenum. When the duodenum moved, the intracholedochal pressure showed continuous and rhythmic rises of 80 to 120 mm. of water, according to the tonic and rhythmic contractions of the gallbladder. The bile was evacuated into the duodenum continuously or intermittently, corresponding to the peak of intracholedochal pressure.

CASE 2.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 11.5 Kg. The observation was made on the thirty-fourth day after operation, May 23, 1936 (fig. 1). As may be seen in figure 5, the movements of the duodenum were periodic. The duodenum, after a resting period of ten minutes, passed into the active phase, at the end of which the tetanic form of activity was observed. Following this came the resting period, of thirty

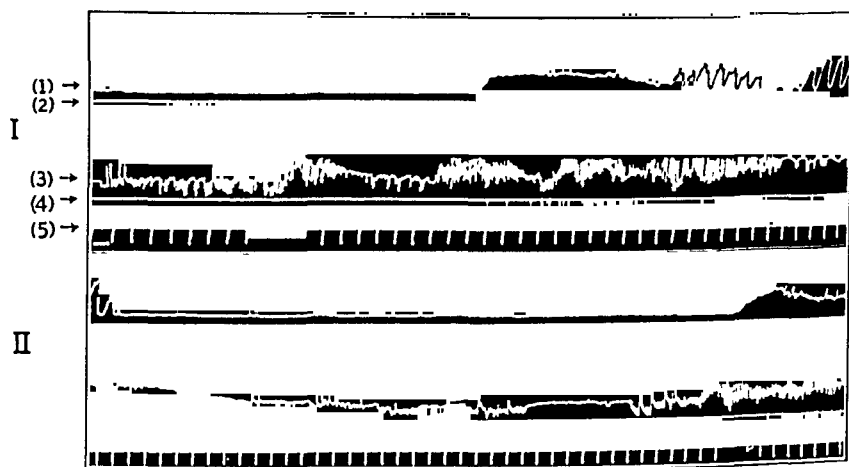


Fig. 4.—I and II are connecting. 1, intracholedochal pressure; 2, zero pressure line; 3, duodenal movement; 4, drop counts of bile evacuation into the duodenum; 5, time (one minute).

minutes; then the second active period, which lasted for about seventy minutes, with another change to the tetanic type of movement. With regard to the evacuation of bile, corresponding to the active periods of the duodenum, there were also frequent spontaneous contractions of the gallbladder and an intermittent rise of the intracholedochal pressure, and, corresponding with this rise in pressure, intermittent evacuation of bile into the duodenum occurred.

Observations were carried out on the same dog the following day, with almost the same results.

CASES 3 and 4.—Investigations by the same methods showed almost similar results.

CASE 5.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 11.5 Kg. The observation was made on the twenty-third day after operation, Nov. 11, 1936 (fig. 2). In this case a record of the changes in resistance at the distal end of the common bile duct was included in the obser-

vations. The outflow of bile and the duodenal movements were found to be the same as in cases 1 and 2. However, the resistance of the sphincter of Oddi during the active phase of the duodenum was 80 to 100 mm. of water pressure. The resistance frequently rose to 120 to 200 mm. of water pressure, and the waves of rising resistance apparently had no relation to the movements of the duodenum. At the beginning of the resting period the resistance was 120 mm., which gradually decreased to 80 mm. at the end of this period, and, moreover, no waves of changes in pressure were observed.

CASES 6 and 7.—The same methods (fig. 2) were used, with almost the same results. However, in case 6 during the active period the resistance of the sphincter of Oddi was 150 mm., with frequent waves of rises in resistance, reaching 180 to 270 mm. In the tetanic period the resistance appeared in several great waves, rising to 400 mm. and always corresponding to the rise of tonus in the duodenum.

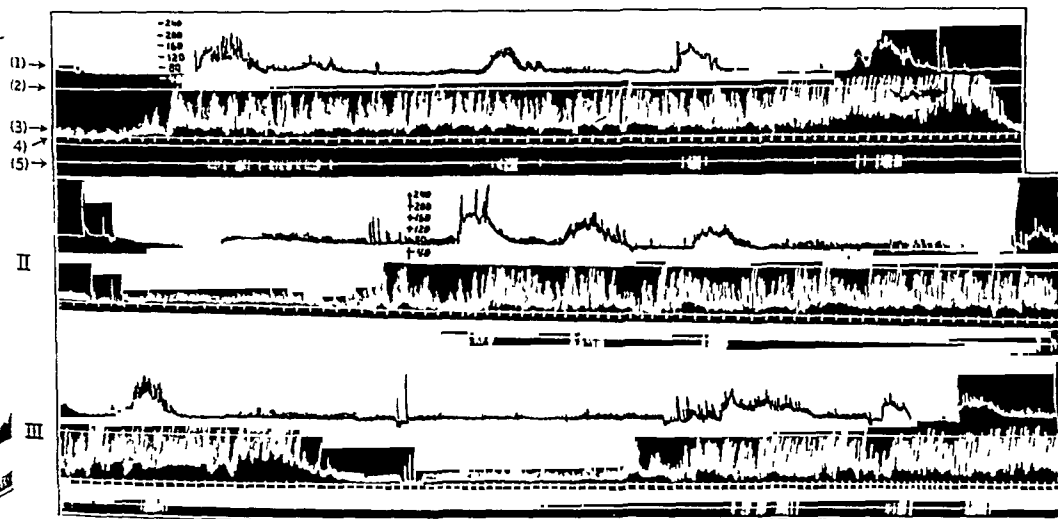


Fig. 5.—I, II and III are connecting. 1, intracholedochal pressure; 2, zero pressure line; 3, duodenal movement; 4, time (one minute); 5, drops of bile evacuation into the duodenum.

With the passing of the duodenal movements into the resting phase, the resistance of the sphincter of Oddi decreased, not suddenly but gradually, from 240 mm. to 150 mm.

In case 7 the resistance of the sphincter of Oddi at the beginning of the experiment (resting period) was 100 mm. of water pressure. There was no evacuation of bile. With the change into the active period the resistance was generally 100 mm., although waves of rises reaching 160 mm. appeared now and again. When the intracholedochal pressure rose the sphincter of Oddi permitted evacuation of bile. However, in the tetanic period great waves of rising resistance (up to about 400 mm.) appeared, which checked the flow of bile.

CASE 8.—Permanent double intubation and a duodenal fistula were instituted. The observation was made on the fourteenth day after operation, March 12, 1937 (fig. 3). In the previous cases it was observed that the discharge of bile into

the duodenum occurred concurrently with the rise of the intracholedochal pressure. In this case the changes in pressure at the distal end of the choledochus and the movements of the duodenum were recorded simultaneously. As may be seen in figure 6, from the first the duodenal movements increased gradually, and after eighty-five minutes tetanic movements appeared, lasting fifteen minutes and followed by a resting period of thirty minutes. Discharge of bile was seen during the active and tetanic periods but ceased in the resting period. The resistance at the sphincter of Oddi at the beginning of the active period was 200 to 240 mm., with intermittent variations reaching 280 to 320 mm. During the tetanic phase of the duodenum the resistance rose, with several high peaks (up to 500 mm.). These peaks were almost coincident with the variations in tonus and movements of the duodenum. During the resting phase of the duodenum the resistance curve showed a gradual decrease from 300 mm. at the beginning to 200 mm. at the end.

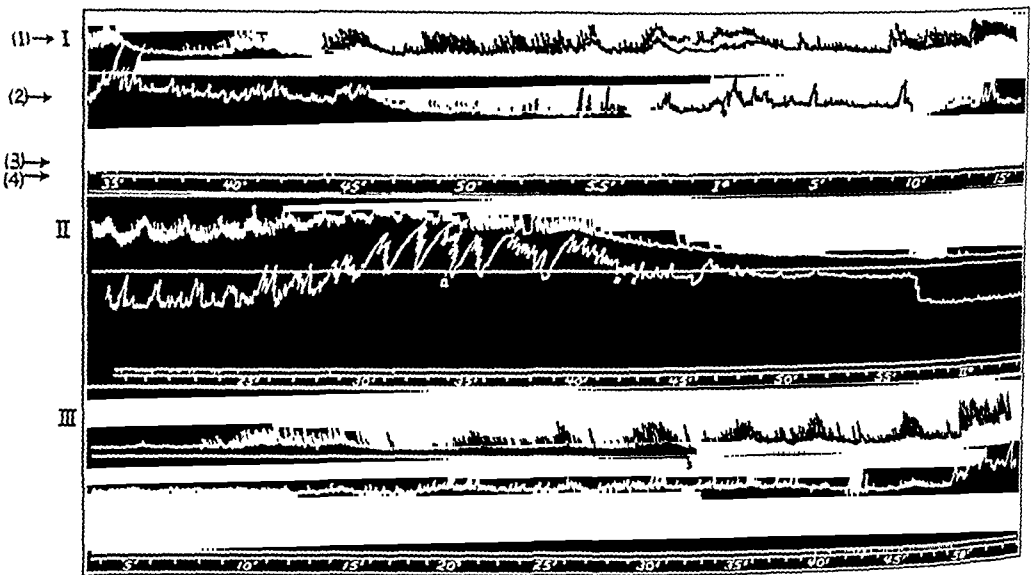


Fig. 6.—I, II and III are connecting. 1, duodenal movements; 2, changes in resistance of the distal part of the common duct; 3, drops of bile evacuated; 4, time (one minute).

#### NONPERIODIC TYPES OF ACTIVITY

CASE 9.—Permanent double intubation and a duodenal fistula were instituted. The observation was made on the thirty-first day after operation, May 23, 1936 (fig. 1). As may be seen in figure 7, throughout the procedure no resting phase of the duodenum was seen. The intracholedochal pressure showed variations according to the rhythmic contractions of the gallbladder, and at the peak of the rise in pressure intermittent evacuation of bile occurred.

CASES 10 and 11.—The results obtained were almost the same as in case 9. In case 10 the intracholedochal pressure showed a minimum pressure of 60 to 80 mm. and irregular rises, reaching 100 to 120 mm., appeared intermittently, with evacuation of bile at the peak of each rise. In case 11 the minimum intracholedochal pressure was 70 mm., varying up to 190 mm., with evacuation of bile.

CASE 12.—Permanent double intubation and a duodenal fistula were instituted. The observation was made on the twenty-second day after operation, Dec. 1, 1936 (fig. 3). In this case records of the changes in pressure at the distal end of the choledochus were made. As is shown in figure 8, the movement of the duodenum was almost continuous, and the resistance at the distal end of the biliary tract

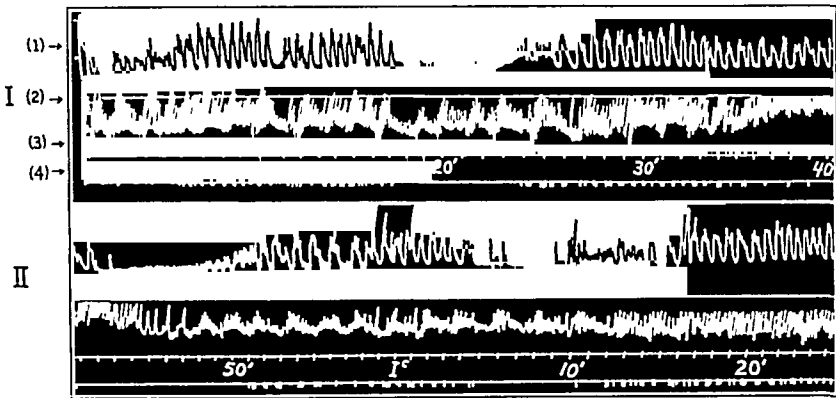


Fig. 7.—I and II are connecting. 1, intracholedochal pressure; 2, movements of the duodenum; 3, time (one minute); 4, bile evacuated into the duodenum.

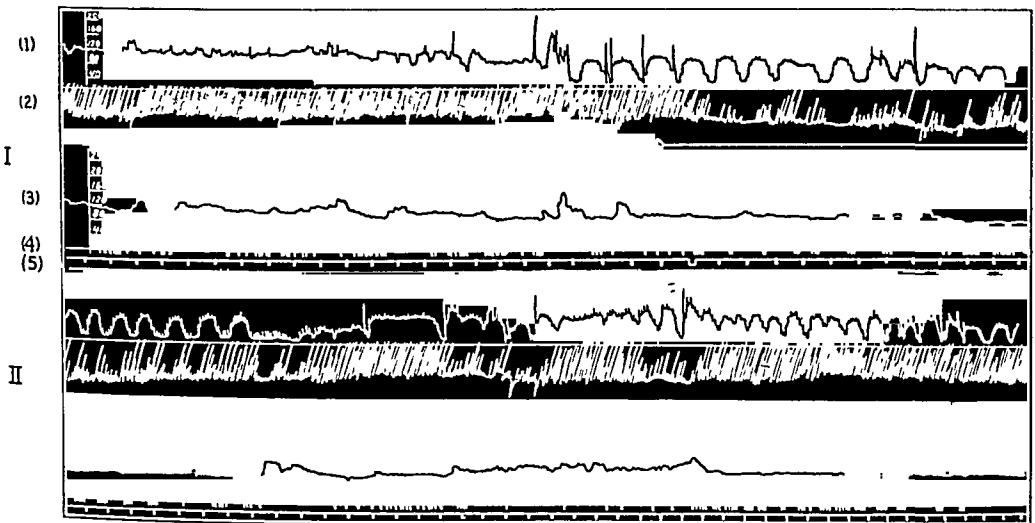


Fig. 8.—I and II are connecting. 1, intracholedochal pressure; 2, movements of the duodenum; 3, changes in resistance at the distal part of the choledochus; 4, drops of bile evacuated into the duodenum; 5, time (one minute).

varied from about 80 mm. to 120 mm. of water pressure. The intracholedochal pressure showed also continuous or rhythmic movement, varying up to about 120 mm. Evacuation of bile took place with the rise in intracholedochal pressure.

This animal was observed again on the twenty-eighth day after operation. and almost the same results were obtained.

## ABNORMAL TYPES OF ACTIVITY

CASE 13.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 12.7 Kg. The observation was made on the twenty-second day after operation, April 15, 1936 (fig. 1). Throughout the four hour period of observation the duodenum showed almost continued activity. The intracholedochal pressure showed rises reaching 200 to 300 mm., with continuous or rhythmic waves; that is, the gallbladder was in a state of restless contraction, notwithstanding the fact that there was no flow of bile into the duodenum.

CASE 14.—Permanent double intubation and a duodenal fistula were instituted. The dog weighed 13.9 Kg. The observation was made on the twenty-first day after operation, Dec. 23, 1936 (fig. 2). As may be seen in figure 9, the duodenum showed restless activity. The intracholedochal pressure also showed variability, reaching 280 to 320 mm., according to the uncertain contractions of the gallbladder. The resistance of the sphincter of Oddi rose to pressures of 320 to 450 mm., which checked the outflow of bile.

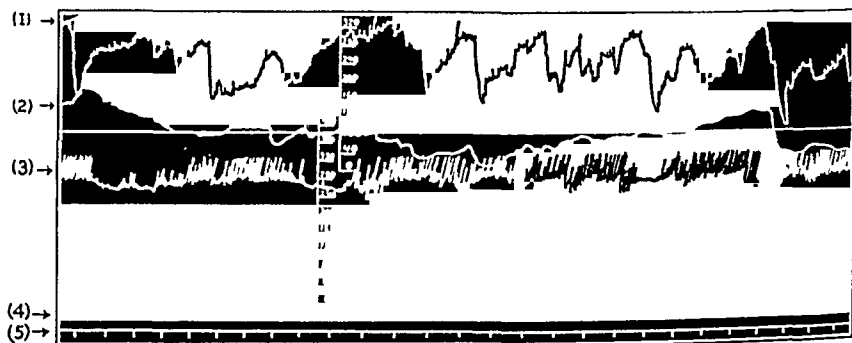


Fig. 9.—1, intracholedochal pressure; 2, changes in resistance at the distal part of the choledochus; 3, movements of the duodenum; 4, bile evacuated into the duodenum; 5, time (one minute).

## SUMMARY

The investigations were carried out 16 times on 14 unanesthetized intubated dogs. In 8 cases a periodic relation between the duodenal movements and the evacuation of bile was seen. In 5 cases nonperiodic types of activity were seen, that is, continuous movement of the duodenum with an intermittent flow of bile. In 2 cases there was no evacuation of bile despite continued movement of the duodenum. The results obtained are almost the same as those of the previous investigations, conducted on man.

In the cases of the periodic type of duodenal movement, during the resting period the intracholedochal pressure showed a continuous decrease of about 30 to 80 mm. of water pressure, according to the relaxation of the gallbladder, and remained almost constant in each case, so that there was no evacuation of bile. During the active phase of the duodenum the intracholedochal pressure became intermittent,



with tonic or rhythmic rises in pressure corresponding to the spontaneous contractions of the gallbladder. At the peak of the tonic or rhythmic rises (120 to 200 mm.) bile flowed into the duodenum, the evacuation being intermittent. Regarding the flow of bile, it is difficult to say at which point in the period of duodenal activity the evacuation is greatest.

The resistance at the distal end of the common duct during the resting phase of the duodenum was 80 to 240 mm., without waves of variation in the pressure. That is, there was gradual decrease from the beginning of the resting period to the end of the period, or to the beginning of the active period. In case 6, starting at 240 mm., the pressure diminished gradually to 150 mm. at the end of the period. In case 8, at the beginning the resistance was about 300 mm., and it decreased gradually to 200 mm. at the end of the resting period.

The resistance during the active period remained about the same as that at the end of the resting period. However, there appeared waves of variation in pressure (120 to 270 mm.). These waves sometimes appeared to have no apparent relation to the tonus of the duodenum, although the contrary was also seen, so that the two relations are probably interchangeable.

When the movements of the duodenum became vigorous and entered the tetanic phase, the resistance at the distal end of the common duct rose with several high waves, reaching 200 to 500 mm. These waves were almost coincident with the variations in tonus and the movements of the duodenum. In the tetanic period evacuation of bile may occur when the waves of resistance are at the weakest.

With the nonperiodic types of duodenal movement the intracholedochal pressure when the gallbladder was relaxed was in some cases 60 to 80 mm. of water. In these cases the rhythmic or tonic pressure waves rose at intervals of ten to twenty minutes, reaching 120 to 160 mm. and varying from several minutes to one-half hour in duration. In other cases the pressure remained continuous, with almost no relaxation period, so that there was intermittent or almost continued evacuation of bile. The resistance at the distal end of the common duct was 80 to 150 mm., with occasional variations ranging from 120 to 300 mm., which might or might not be concurrent with the tonus and the duodenal movements.

With the abnormal types of activity, despite the almost continuous movements of the duodenum there was no evacuation of bile. In these cases the intracholedochal pressure was seen to be irregular, with great variations (200 to 300 mm.), according to the incessant contractions of the gallbladder, while the resistance at the distal end of the common duct appeared over 320 mm., with waves reaching 500 mm. of water pressure.

# ANOMALY OF THE RIGHT INFERIOR LARYNGEAL NERVE

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Injury of the inferior, or recurrent, laryngeal nerve is a definite hazard when subtotal thyroidectomy is performed. Knowing the anatomic variations to which this nerve may be subject near the inferior pole of the thyroid gland, the surgeon is forearmed and may avoid wounding the nerve. Occasionally, notwithstanding consummate care, homolateral paralysis of the vocal cord will be found after completion of the operation. Some unexplained injuries may be accounted for by an anomalous derivation of the inferior laryngeal nerve.

Origin of the inferior laryngeal nerve from the cervical portion of the vagus nerve is uncommon. Recently, during the performance of subtotal thyroidectomy by one of us (Pemberton) the right inferior thyroid artery was ligated in the usual manner just proximal to its entrance into the thyroid gland. At this time the inferior laryngeal nerve was seen to arise from the vagus nerve (fig. 1) and to pass directly behind the internal jugular vein and common carotid artery and then pursue the usual course of the recurrent nerve. This is the fifth instance in which such an anomaly has been observed by the same operator; the first case has been previously reported.<sup>1</sup>

## EMBRYOLOGIC CONSIDERATIONS

The explanation for the anomaly is found in the embryologic development of the primary aortic arches. Pertinent to the subject is the disposition of the fourth, fifth and sixth arches. It will be recalled that the fourth right arch forms the right subclavian artery as far as the source of its internal mammary branch, whereas the fourth left arch constitutes the arch of the aorta between the origin of the left common carotid artery and the termination of the ductus arteriosus. The fifth arches are but transitory and connect the ventral aorta with the dorsal

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1. Pemberton, J. deJ., and Beaver, M. G.: Anomaly of Right Recurrent Laryngeal Nerve, Surg., Gynec. & Obst. **54**:594-595 (March) 1932.

parts of the sixth pair of arches. True fifth arches are probably not always developed, but when they occur they become manifest later in embryonic development and are imperfect. In order to adhere strictly to existing nomenclature, the fifth pair will be included in the total number. Only the sixth right arch vanishes; the sixth left arch gives origin to the pulmonary arteries and forms the ductus arteriosus, the latter normally becoming impervious a few days after birth.

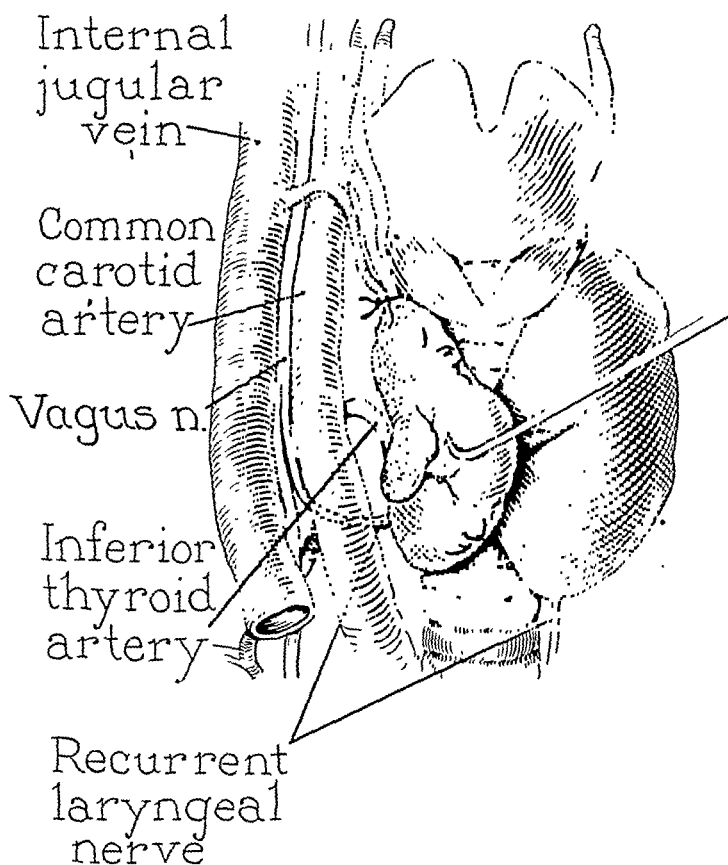


Fig. 1.—Anomalous origin of the right recurrent laryngeal nerve as found at operation.

It will further be recollected that the heart originally lies immediately behind the stomodeum but with elongation of the cervical region and development of the pulmonary apparatus recedes into the thorax. Consequently, the original position of the last three arches is considerably modified. On the right side the fourth arch is then found in the root of the neck, whereas on the left the fourth arch is within the thorax proper. If the transitory fifth arch is included among the primitive arches, the recurrent nerve thus passes under the sixth arch to the larynx. Because of this position the recurrent nerves are pulled caudally

as a result of the descent of the sixth pair of arches. Because of the disappearance of the fifth branchial arch on the left and of the fifth and sixth on the right, the left recurrent nerve proceeds around the obliterated ductus arteriosus, whereas the right encircles the fourth, or subclavian, arch (fig. 2). Thus, when the inferior laryngeal nerve is not found to be "recurrent," a correlative arterial anomaly involving the subclavian artery is also present. In 1899, Holzapfel<sup>2</sup> made an exhaustive review of such abnormally derived vessels. He reported that in 3 cases the inferior laryngeal nerve looped around the anomalously derived artery, whereas in 4 others the nerve passed around the right vertebral artery, which in these cases was a branch of the right common carotid

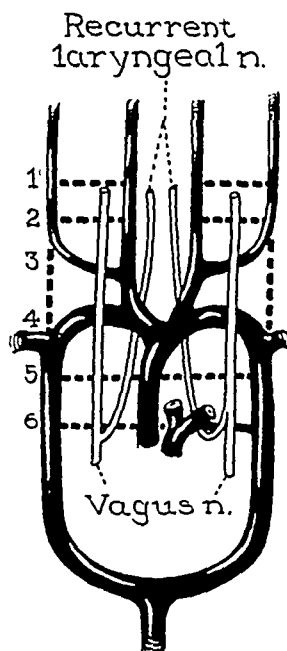


Fig. 2.—Normal relations between the primary aortic arches (1, 2, 3, 4, 5 and 6) and the recurrent laryngeal nerves.

artery. In the remaining 28 cases and in all others found by Williams<sup>3</sup> in the recent literature, the nerve is described as originating from the vagus at the level of the larynx and passing behind the right common carotid artery to its normal distribution.

Williams and others<sup>4</sup> have examined the aortic arch in 159 persons and have found an anomalous right subclavian artery in 4 instances

2. Holzapfel, G., cited by Williams.<sup>3</sup>

3. Williams, G. D.: Anomaly of the Inferior Laryngeal Nerve, *Ann. Surg.* 97:828-830 (June) 1933.

4. Williams, G. D.; Aff, H. M.; Schmeckebier, M.; Edmonds, H. W., and Gaul, E. G.: Variations in the Arrangement of the Branches Arising from the Aortic Arch in American Whites and Negroes, *Anat. Rec.* 54:247-251 (Oct.) 1932.

(2.6 per cent). This figure is somewhat greater than those given by other authors, whose reported incidences are between 0.2 and 2 per cent.

#### ANATOMIC CONSIDERATIONS

With the foregoing embryologic facts in mind, the cervical derivation of the right inferior laryngeal nerve may be explained logically. Atrophy of the fifth and sixth arches on the right occurs normally. However, in the cases under consideration the right fourth arch, between the derivations of the common carotid and subclavian arteries, also vanishes. The inferior laryngeal nerve is not drawn caudally and will be found arising

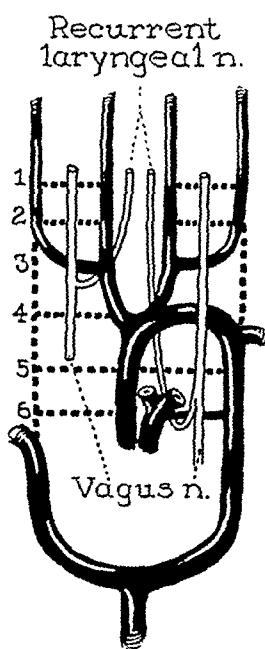


Fig. 3.—Origin of the inferior laryngeal nerve in the cervical region; 1, 2, 3, 4, 5 and 6, primary aortic arches.

from the vagus nerve at the level of the larynx (fig. 3). Interesting, too, is the mode of origin of the subclavian artery in such cases. An innominate artery is lacking, and the great vessels arise from the aortic arch in the following order: right common carotid, left common carotid, left subclavian and right subclavian. The last vessel originates most commonly near the junction of the transverse and descending portions of the aorta (fig. 4). It then passes obliquely upward and to the right, anterior to the vertebrae and posterior to the trachea and esophagus, to the root of the neck. For blood to reach the right subclavian artery from the aorta it is necessary that it pass along that portion of the right fourth arch which intervenes between the origin of the subclavian artery

and the point at which the two aortic roots join to form the secondary trunk of the aorta. The right aortic root remains pervious, instead of disappearing as is usual. Consequently, the first portion of the anomalous right subclavian artery consists of a persistent right aortic root.

Variations of this circumstance (Piersol<sup>5</sup>), depending on the exact site and extent of the disappearing portion of the right fourth arch, may also modify the relation existing between the subclavian artery and its vertebral branch. The vertebral artery may arise from the subclavian artery, the aorta or even the common carotid artery. An explanation for the 4 cases of Holzapfel in which the right recurrent nerve passed around the vertebral artery is thus obtained. The vessel which is destined to be the common carotid is the artery of the third branchial

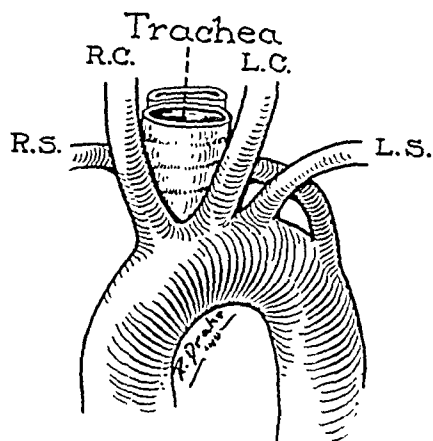


Fig. 4.—Anomalous origin of the right subclavian artery from the junction of the transverse and descending portions of the aorta.

arch. Since the right fourth, fifth and sixth arches have disappeared, the nerve passes around the third arch. Since the vertebral artery may be a branch of the carotid artery, the nerve must wind around both vessels, and thus it hooks around the vertebral artery.

A cervical origin of the left inferior laryngeal nerve is found much less frequently than is a like origin of the right inferior laryngeal nerve, because of the extremely complex relation that must exist to permit its occurrence. When the right fourth arch persists, the left fourth arch disappears and the aorta passes over the root of the right lung, that is, directly opposite to its usual course, the great vessels arising from the aorta are arranged in a manner opposite to that previously described. The left common carotid, the right common carotid, the right subclavian

5. Piersol, G. A.: *Human Anatomy*, ed. 9, Philadelphia, J. B. Lippincott Company, 1930.

and the left subclavian arteries arise in that order. This is not a true situs inversus viscerum but merely a reversal of the aortic arch and its branches. With atrophy of the fourth left arch between the derivations of the left common carotid and the left subclavian artery, the distal portion of the arch persists and forms the first portion of the subclavian artery. The process is an exact counterpart of the derivation of an anomalous subclavian artery on the right.

Variations of this anomaly concern principally the relations of the ductus arteriosus, or ligamentum arteriosum. It may unite with the descending aorta, in which case the ductus is derived from the right

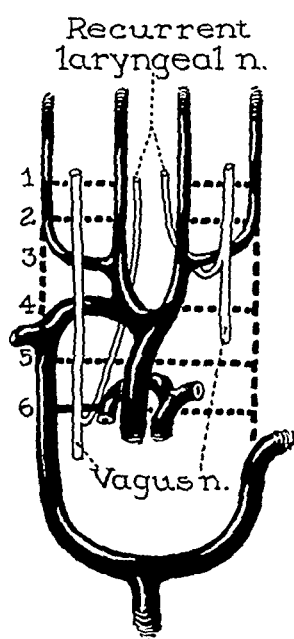


Fig. 5.—Origin of the inferior laryngeal nerve in the cervical region. This represents true transposition of the vessels and nerves as shown in figure 3; 1, 2, 3, 4, 5 and 6, primary aortic arches.

sixth branchial vessel, or it may originate, as usual, from the left sixth branchial vessel, communicating with the left subclavian artery. When the ductus arteriosus is on the right and the left subclavian artery is found to arise from the descending aorta, the left inferior laryngeal nerve will not be drawn into the thorax, for the left fourth, fifth and sixth arches have vanished (fig. 5). If, however, the ductus arteriosus has its origin from the left sixth branchial vessel and communicates with the homolateral subclavian artery, the inferior laryngeal nerve will be found in the thorax.

If true transposition of the viscera is present, the ductus arteriosus will be formed from the right sixth branchial vessel. If, in addition to

this anomaly, the left fourth arch vanishes and the left subclavian artery is derived from the descending aorta, the inferior laryngeal nerve will arise in the neck, since the left fourth, fifth and sixth arches have disappeared and the nerve will not be drawn caudally.

#### SUMMARY

The practical surgical value of recognition of the occasional cervical origin of the "recurrent" laryngeal nerve is apparent. Blunt dissection lateral to the thyroid gland must be undertaken with care. In addition, if ligation of the inferior thyroid arteries external to the gland is contemplated, the vessels should be carefully isolated and visualized to avoid passing a ligature around the artery and the nerve together. In addition, an artery forceps must not be carelessly applied lateral to the thyroid gland, because of the danger of crushing the nerve. These accidents may explain a few of the heretofore unaccountable cases of paralysis of the vocal cords.



# PROGRESSIVE BACTERIAL SYNERGISTIC GANGRENE

## INVOLVEMENT OF THE ABDOMINAL WALL; REPORT OF AN UNUSUAL CASE

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Progressive bacterial synergistic gangrene is a chronic, rapidly spreading necrosis of the skin characterized by a distinct clinical picture and caused by a symbiosis of organisms, the cultural characteristics of which have been described by Meleney.<sup>1</sup> The disease is rare, although since 1924 an increasing number of case reports have appeared in current medical literature. Because of its infrequent occurrence it may not be recognized when first seen. The disease is so distressing to the patient and so persistent in its relentless destructive process that it is of the utmost importance that an early diagnosis be made and proper treatment instituted.

### HISTORICAL CONSIDERATIONS

In 1909, Luckett<sup>2</sup> reported an unusual, rapidly spreading ulcer of the abdominal wall, which developed from a pimple. Removal of the scab, which followed picking of the pimple, revealed a small ulcer. Within six days this ulcer enlarged to 2 by 3 inches (5 by 7.6 cm.). Twelve days later it measured 5¼ by 10¼ inches (13.3 by 26 cm.) and had destroyed most of the skin covering the lower part of the abdomen. The usual local remedies were tried, but none of them were of any help in controlling the spread of the disease. Finally, the entire lesion, including a zone beyond the area of inflammation, was excised with the cautery. Complete and rapid recovery resulted.

Cullen<sup>3</sup> in 1924 described a "progressively enlarging ulcer of the abdominal wall involving the skin and fat, following drainage of an

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1. Meleney, F. L.: Bacterial Synergism in Disease Processes, with a Confirmation of the Synergistic Bacterial Etiology of a Certain Type of Progressive Gangrene of the Abdominal Wall, *Ann. Surg.* **84**:961, 1931.

2. Luckett, W. H.: Large Phagedenic Ulcer of the Abdomen, *Ann. Surg.* **50**:605, 1909.

3. Cullen, T. S.: Progressively Enlarging Ulcer of Abdominal Wall Involving Skin and Fat Following Drainage of an Abdominal Abscess Apparently of Appendiceal Origin, *Surg., Gynec. & Obst.* **38**:579, 1924.

abdominal abscess apparently of appendiceal origin." In the same year Christopher<sup>4</sup> recorded his experiences with a "severe spreading carbuncular infection of the chest wall following rib resection."

In an interesting study, Bartlett<sup>5</sup> found that the older medical literature contains numerous accounts of enormous spreading ulcers of the skin, some of which appear to be identical with these lesions. The interest of modern surgeons, however, appears to date from the reports by Cullen and Christopher.

In 1926, Brewer and Meleney<sup>6</sup> reported a case similar to that reported by Cullen. Of special interest was the bacteriologic study, which pointed out the peculiar relation between the organisms concerned in the development of this disease. In 1931 Meleney<sup>7</sup> reported further studies confirming the synergistic bacterial causation of a certain type of progressive gangrene of the abdominal wall. These reports established the disease as a clinical entity and made possible an early accurate diagnosis.

In 1935, Stewart-Wallace<sup>8</sup> reported a case of gangrene of skin and subcutaneous fat following thoracotomy for drainage of an empyema similar to that in the case reported by Christopher. The gangrene progressed for eight months, at the end of which time it involved the back, from the occiput to the iliac crest, and the whole of the anterior abdominal surface. The patient died. In a recent report Vier<sup>9</sup> stated that a review of the literature at present reveals fewer than 40 authenticated case reports. One or more cases have been reported respectively from England, Japan, Sweden, Germany, Italy and Australia, although the vast majority have been reported from the United States. An extensive bibliography was given by Hirshfeld.<sup>9</sup>

#### CLINICAL PICTURE

Gangrene of the skin usually follows drainage of an abscess. The involved area becomes exceedingly tender, red and swollen. The wound

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4. Christopher, F.: Severe Spreading Carbuncular Infection of Chest Wall Following Rib Resection Under Local Anesthesia, *S. Clin. North America* 4: 795, 1924.

5. Bartlett, A. V.: Studies on Phagedenic Ulcers, Thesis, Yale University School of Medicine, 1938.

6. Brewer, G. C., and Meleney, F. L.: Progressive Gangrenous Infection of Skin and Subcutaneous Tissues Following Operation for Acute Perforative Appendicitis: A Study in Symbiosis, *Ann. Surg.* 84:438, 1926.

7. Stewart-Wallace, A. M.: Progressive Post-Operative Gangrene of the Skin, *Brit. J. Surg.* 22:642, 1935.

8. Vier, H. J.: Progressive Post-Operative Gangrene of the Abdominal Wall, *Surgery* 7:334, 1940.

9. Hirshfeld, J. W.: Phagedenic Ulcer, *Surgery* 5:894, 1939.

margins or the stitch holes become indurated, and the swollen area becomes purplish. Beyond this purple zone is a bright red zone, which passes into the normal skin. Within a few days the purplish areas widen and the part first affected becomes gangrenous. The color of the dead skin changes to a dirty grayish brown, and the surface is dull like suede leather. The purple zone spreads outward into the red, and as it does so the skin becomes raised above the normal level. The central side of the purple zone, toward the gangrene, is sharply defined but irregular and crenated. On the outer side it fades off into the red zone and flattens to the level of the normal skin. The gangrenous skin remains firmly adherent to the purple zone and becomes undermined at its free margin, but there is little if any undermining of the normal skin. As the process advances the gangrenous skin liquefies on its inner margin, leaving exposed a base of granulation tissue which gradually enlarges.

#### ETIOLOGY

The lesion is associated with a specific bacterial causation. This was clearly established by Brewer and Meleney<sup>6</sup> and confirmed in subsequent studies by Meleney<sup>1</sup> and Willard.<sup>10</sup> When careful anaerobic and aerobic methods of bacterial culture are employed, a micro-aerophilic non-hemolytic streptococcus<sup>11</sup> may be found in pure culture at the periphery of the lesion, not only in the red zone but occasionally just beyond it, in the relatively normal tissue. In the gangrenous tissue itself this streptococcus is associated with an aerobic hemolytic *Staphylococcus aureus*. That either organism alone is incapable of producing this lesion has been demonstrated. Pure cultures of either organism injected into animals result in no ulceration, but when the two organisms are combined in one-half the dose of each used separately a gangrenous process usually develops.

"The demonstration that these organisms can do something together which they cannot do alone suggests that the disease is the result of a synergistic action of the organisms, the non-hemolytic micro-aerophilic streptococcus being the essential organism in the zone of advance and in some way preparing the ground for the gangrenous action of the combined organisms. The streptococcus is most likely derived from the intestinal canal, while the staphylococcus may come from the patient's skin or from the air" (Meleney).

10. Willard, H. G.: Chronic Progressive Post-Operative Gangrene of the Abdominal Wall, *Ann. Surg.* **104**:227, 1936.

11. The micro-aerophilic streptococcus is one of a group which occurs frequently in the human intestine and in peritoneal exudates. It prefers an anaerobic environment and for the first cultivation must be obtained by anaerobic methods. However, after several transplantations on artificial mediums the organisms will grow on aerobic mediums as well.

## DIFFERENTIAL DIAGNOSIS

Meleney<sup>12</sup> has called attention to the importance of making a prompt differential diagnosis between the various types of infectious gangrene of the skin, because the treatment of the different types varies markedly and early institution of the proper treatment not only may save life but will decrease the cicatrization and deformity. Four types of chronic gangrene of the skin due to infection have been described.

Progressive bacterial synergistic gangrene can be differentiated by its specific causation and its characteristic clinical picture. The absence of any constitutional disturbance except the effects of pain on the well-being of the patient and the presence of the local excruciating pain associated with the characteristic appearance of the ulcer make the clinical diagnosis evident. The demonstration of the hemolytic *Staph. aureus* in aerobic culture and of nonhemolytic streptococci when the latter can be grown in an anaerobic culture establishes the specific nature of the disease. The uselessness of all forms of therapy other than complete excision, as far as the present status of this disease is concerned, is established.

Amebic infection with gangrene may follow the drainage of an amebic abscess of the liver. Amebas may be found in the stool but are numerous in the exudate of the wound and in the tissue. Specific therapy for amebiasis is indicated.

Gangrenous impetigo is usually associated with hemolytic streptococci and staphylococci. The lesions are usually multiple and may coalesce but are seldom large. Arising as vesicles, they soon pustulate and become gangrenous. Adequate treatment requires removal of crusts and intensive local application of ammoniated mercury ointment in addition to general nutritional treatment.

Fusospirochetal gangrene usually occurs in a wound contaminated with oral secretions, such as the bite of a human being. The essential organisms are fusiform bacilli, spirilla and spirochetes, often associated with nonhemolytic streptococci.

In only one of the four types of chronic infectious gangrene—progressive bacterial synergistic gangrene—is the micro-aerophilic nonhemolytic streptococcus present. Other conditions that must be differentiated are the chronic undermining ulcer and acute infectious gangrene.

The chronic undermining ulcer develops slowly, with liquefaction of the subcutaneous fat. The skin may take on a dull red or bluish appearance, thin out and develop a small opening, which enlarges until the margin fuses with the original ulcer. There is no gangrene of the skin with this type of ulceration. Moderate pain is present. The micro-aerophilic streptococcus can be grown from this lesion anaerobically. The use of zinc peroxide causes rapid healing of the process.

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12. Meleney, F. L.: A Differential Diagnosis Between Certain Types of Infectious Gangrene of the Skin, *Surg., Gynec. & Obst.* 56:847, 1933.

The acute forms of infectious gangrene are differentiated by their rapid spread. In cases of gangrene due to the hemolytic streptococcus the onset is insidious. Redness and swelling followed by blister formation and the development of areas of gangrene within a week is characteristic. The gangrenous area is irregular, not sharply defined and associated with intense necrosis of the connective tissue. Bacteriologic examination shows a pure growth of streptococci.

Gangrene due to erysipelas starts usually with a chill and high fever. The area of redness is sharply defined and well localized. Acute infectious gangrene must be differentiated from this condition because of the need of prompt multiple incisions to lessen the tension and provide drainage of the area of gangrene due to the hemolytic streptococcus. In cases of erysipelas such radical treatment is not necessary.

Gas gangrene can be recognized by the gas formation in the tissues and the bacterial flora observed on anaerobic cultivation.

#### TREATMENT

Up to the present time neither local applications to the ulcer nor partial excision within the outer, red zone of the lesion has been found to be of value in the cure of this disease. Systemic treatment too has not been of any use in the cases so far reported. Complete excision of the lesion, including a zone of normal tissue about the periphery of the red zone, down to the deep fascia actually removes the disease. The application of zinc peroxide cream<sup>13</sup> to the wound after excision inhibits growth of anaerobic organisms that may be deposited in or may have remained in the wound. This is necessary, since organisms have been found in the normal tissues beyond the red zone. The covering of the defect with skin grafts after a clean granulating surface has been obtained makes early healing possible and diminishes scar tissue formation.

#### REPORT OF CASE

A man 50 years of age was operated on July 2, 1937, forty-eight hours after the onset of symptoms of acute appendicitis. The localization of pain and tenderness

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13. Effective zinc peroxide depends on the ability of the powder to evolve oxygen gas when suspended in distilled water. This effective material must be applied to all parts of the wound as a creamy suspension, and evaporation must be prevented by sealing the whole dressing with petrolatum or zinc oxide ointment. The powder is sterilized in convenient quantities of 10 to 50 Gm. in glass tubes. The content of one or more tubes is then thoroughly mixed by means of a syringe with enough distilled water to give an even creamy suspension about the consistency of 40 per cent cream. Effective material will usually be found to swell somewhat in the water, so that it thickens, and more water may have to be added during the course of the dressing. A thick paste is undesirable, since it will not flow freely into the recesses of a wound.

in the rectum, indicating a pelvic location of the appendix, warranted the use of a right paramedian incision instead of the usual muscle-splitting incision. An acutely inflamed gangrenous appendix was removed after the abdominal wound had been carefully walled off. The abdominal wall was closed in layers and healed by primary union. Sutures in the skin were removed on the tenth postoperative day, and the patient was discharged from the hospital four days later (July 16). On the seventeenth postoperative day (July 19), while at home, the patient noted a "pimple" to the left of and above the umbilicus. During the next two weeks this took on the appearance of a carbuncle, enlarged rapidly and sloughed in its central portion, leaving an ulcer with a necrotic edge. The use of warm moist compresses, sterile dressings and dry heat locally did not relieve the intense pain associated with this lesion, nor did the lesion show any tendency to cease spreading. The patient returned to the hospital on August 4. Physical examination showed the essential pathologic process to be limited to the abdominal wall. A necrotic, ulcerated lesion was located about the umbilicus, but the umbilicus was not involved in the necrotizing process. The lesion measured approximately  $7 \times 10$  cm. in its axes and was 2 cm. deep. The central zone was a granulating surface. The edge of the ulcer had an overhanging margin of necrotic skin, dark yellow-gray, beneath which there exuded a thick purulent discharge. This rim varied in width from 1 to 3 cm. and was bounded on its outer border by a dark purple zone 2 to 3 mm. in width, with a dentate appearance. Beyond this was a zone of redness 2 to 3 cm. in width, which faded into the normal skin. The scar of the recent abdominal wound was well healed, and the ulcer did not invade this scar. Toward the upper end of the scar, at the site of a previously healed suture puncture wound, there appeared a watery discharge, but it was undecided whether this came from the adjacent ulcer or from the fat beneath the scar of the healed wound. Direct smears from the lesion showed many gram-positive coccic forms and a few short chain streptococci. Cultures in broth on aerobic mediums showed few streptococci and numerous staphylococci.

It was thought that a communication existed between the depth of the original wound and the spreading ulcer and that hidden infection served to initiate and continue the periumbilical infectious process. On August 4, with the patient under ethylene-oxygen anesthesia, the entire necrotic zone of the ulcer was excised and the upper portion of the recent abdominal wound was incised. No communication was found between the ulcer and the depths of the healed wound. The watery discharge noted previously was scant and lay adjacent to the umbilicus, in a space which appeared to communicate with the ulcer. The granulating surface was well irrigated with hydrogen peroxide and covered with sterile dressings. Between August 5 and August 19 the ulcer continued to spread and the pain persisted in its former intensity. The latter had a detrimental effect on the patient's well-being, as it resulted in a depressed mental state. A variety of local applications were employed, without curative effect. Potassium permanganate irrigations and dressings, potent zinc peroxide in distilled water, diluted solution of sodium hypochlorite U. S. P. (Dakin's solution), moist boric acid compresses and dry heat successively failed to curb the spread of the ulcer, but the upper portion of the old wound, which had been incised, did not become involved in the ulcerative process. Ninety grains (5.8 Gm.) of sulfanilamide was given during thirty-six hours, but the cyanosis, acute distress and sudden weakness of the patient prompted discontinuance of this medication. Aerobic cultures made from the wound exudate on August 16 showed staphylococci. Anaerobic cultures made on August 19 showed small diplococci, streptococci and staphylococci. Further identification of the

organisms was not made. A study of the literature made it increasingly evident that this case (fig. 1) corresponded accurately with the picture of the disease entity described by Meleney and called by him "progressive bacterial synergistic gangrene." When this was realized, on August 19, two weeks after the patient's readmission to the hospital, he was reoperated on, with ethylene-oxygen anesthesia, and the whole lesion was excised. Cessation of all symptoms was evident soon after excision of the lesion. The excised tissue included an outer zone of normal skin 2 cm. beyond the red zone and extended down to the deep fascia. This wound was covered with a cream made of sterile potent zinc peroxide in distilled water and



Fig. 1.—Progressive bacterial synergistic gangrene. *A*, umbilicus; *B*, incision into the original wound; *C*, granulating surface, *D*, necrotic zone; *E*, purple zone, *F*, elevated red zone

was overlaid with sterile gauze saturated with the same material. Similar dressings were applied each day. A clean granulating surface developed, and twelve days after excision of the ulcer Thiersch grafts taken from the thigh under local anesthesia were placed along the periphery of the granulating wound. Because of personal circumstances the patient left the hospital on September 4. He was persuaded to return for complete skin grafting of the granulating surface. Intermediate thickness grafts were applied, but a sudden acute mental episode resulted

in dislocation of the dressings and sponges used for compression. Some of the grafts were lost, but healing eventually took place, with some scar formation on December 4. Recovery was complete (fig. 2).

#### COMMENT

This case illustrates several unusual features of this disease. The sequence of events points out the need for a prompt and thorough bacteriologic study to establish the identity of the disease early in its existence. While in most instances the disease has followed drainage of an



Fig. 2.—The healed wound. *A* and *B* have the same significance as in figure 1.

abscess, in the present instance no abscess was drained. The lesion arose independently of the incision in the abdominal wall, and despite its rapid spread it did not invade this incision. It is likely that tissue injury or tissue tension is necessary for establishment of the organism in the tissue. In many reported cases the disease developed about tension sutures. It is possible that the organisms associated with the disease may be present on the cutaneous surface and may enter the skin through some wound caused by a towel clip puncture wound, a scratch, an abrasion or a defect caused by removal of adhesive tape. While none of these could be



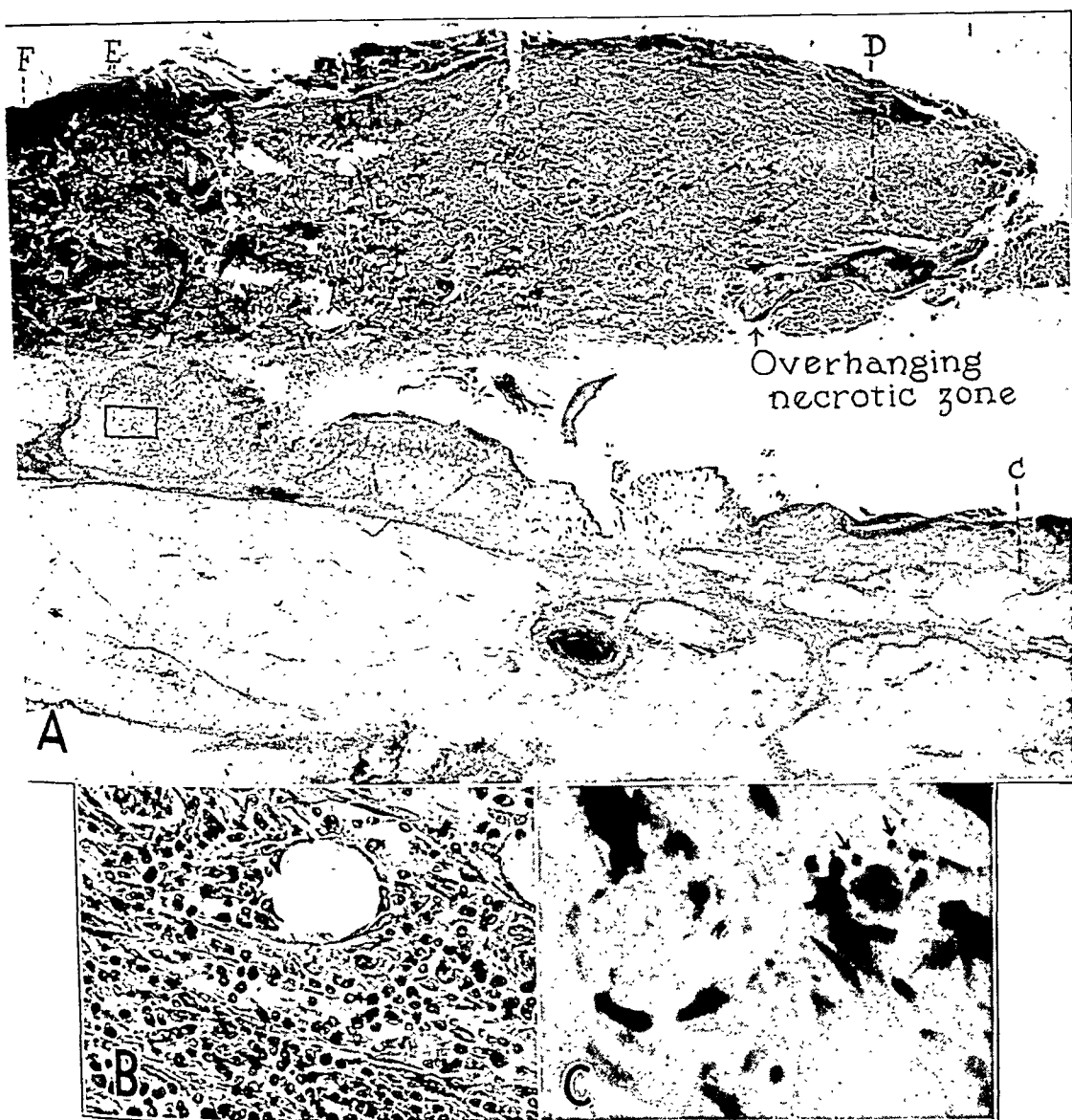


Fig. 3.—*A*, low power photomicrograph showing the margin of the ulcer composed of necrotic tissue. Note the infiltration (*D*) with large numbers of inflammatory cells. *B*, high power photomicrograph within the zone marked in *A*. The fat tissue is the site of dilated capillary blood vessels and large numbers of inflammatory cells. *C*, organisms stained with safranin in the red zone. These do not appear clearly in the photomicrograph, because the sections available for staining were too thick. When brought into accurate focus at different levels in the microscope, biscuit-shaped diplococci showed clearly.

established as having existed in the present instance, they remain as possibilities which should be avoided. The case parallels that reported by Luckett in 1909.

The reason for failure of all forms of therapy other than excision becomes obvious when it is realized that the organisms responsible for this disease are located deep in the tissues in the outer red zone. All applications which inhibit anaerobic bacterial growth fail to make contact with these organisms. Local excision of the necrotic zone alone fails to expose these organisms. The need for removal of a zone of normal tissue beyond the red zone is indicated by the finding of organisms here. A creamy suspension of potent zinc peroxide is necessary to flow freely into every exposed surface in order to destroy or inhibit the organisms that may still remain in the exposed wound surface.

#### PATHOLOGIC PICTURE

The gross appearance of the lesion is characteristic. Necrosis of the dermis appears to succeed destruction of the superficial layer of fat. In the present instance it is noteworthy that the umbilicus remained uninvolved throughout the course of the disease. The absence of fat in this area may account for its preservation. The old scar of the abdominal wound was not invaded by the organisms. It is likely that the scar tissue here prevented involvement of the subcutaneous fat by serving as a barrier to invasion. On microscopic section (fig. 3 *A*) the margin of the ulcer was seen to be composed of large numbers of polymorphonuclear leukocytes, chromatin debris and islands of swollen and edematous epidermis. The blood vessels in this area were dilated and engorged, and throughout were extravasations of red blood cells. The epidermis proper, which began about 2 cm. from the edge of the ulcer, was swollen, and the subepithelial tissue was the site of a dense accumulation of polymorphonuclear leukocytes which invaded and separated the bundles of elastic tissue. These infiltrations extended deep into the subcutis and were most marked about the blood vessels. In the deeper portions of the subcutaneous fat tissue were focal accumulations of polymorphonuclear leukocytes, lymphocytes and small round cells (fig. 3 *B*). Organisms could be seen (safranin stain) in the red zone (fig. 3 *C*). These appeared as diplococci. Meleney<sup>12</sup> has demonstrated large numbers of cocci in the red zone. These are well illustrated in his publications.

#### SUMMARY

A case of progressive bacterial synergistic gangrene is presented. Since the specific bacteriologic causation of this lesion has been conclusively demonstrated, an adequate bacteriologic study made early in the course of the disease would have been advantageous in establishing

the specific identity of the lesion. The publications of Meleney give in detail the interesting bacteriologic studies made of this disease. The appearance of the ulcer, with its margin of three zones, is characteristic. The present case differs from most other reported cases of the same disease in that the lesion did not commence at or involve the laparotomy wound or the sites where tension sutures were employed. The umbilicus, although completely encompassed, was not "consumed." The disease is a chronic specific ulceration associated with gangrene of the skin and must be differentiated from other types of chronic ulceration and other types of gangrene. Up to the present time recovery from this disease has been due in every instance to complete excision of the lesion, including a zone distal to the outer red margin. While the cautery has been recommended, excision by scalpel has proved satisfactory.

# TREATMENT OF TUBERCULOSIS OF THE SHOULDER

## A STUDY OF END RESULTS

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Some uncertainty exists as to the most suitable treatment for tuberculosis of the shoulder in adults. This is due partly to the relative rarity of this condition and partly to the inadequate follow-up after treatment. In the case of children the problem seems simpler, because there is almost complete agreement that treatment should be conservative. In this paper treatment will be evaluated on the basis of the experience at the Lakeville State Sanatorium.

Since tuberculosis is a systemic illness with local manifestations, the general treatment of the patient is of great importance. If possible, a period of sanatorium care should be instituted before operative procedures are undertaken. Fresh air, an adequate and balanced diet and regular rest periods are important in restoring the patient to his optimum physical condition. Immobilization of the affected shoulder in a plaster cast is orthodox therapy.

For children a long period of conservative treatment is imperative. By early operation the humeral epiphysis may be interfered with and the growth of the arm seriously impaired. Magnussen<sup>1</sup> treated 7 children conservatively by plaster immobilization and obtained a useful joint in every case.

Allard<sup>2</sup> recommended that a general anesthetic be administered if necessary and a plaster cast applied with the arm in abduction.

The conservative treatment per se is of limited value for adults. Graber-Duvernay<sup>3</sup> reported good results in 2 cases in which heliotherapy (in a revolving solarium) was combined with active motion. These results require confirmation and are in contradiction to the

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From the Massachusetts Department of Public Health and the Lakeville State Sanatorium.

1. Magnussen, R.: Seven Cases of Tuberculosis of the Shoulder in Children, *Nord. med. tidskr.* **10**:1420, 1935.

2. Allard, L.: L'ostéotomie sous-tubéreuse dans la scapulargie de l'enfant, *Rev. méd. franç.* **16**:835-837 (Dec.) 1935.

3. Graber-Duvernay, J.: Deux observations de carie sèche de Volkmann, *Résultats thérapeutiques*, *Bull. méd., Paris* **48**:341-344 (May) 1934.

present teaching that the treatment of choice is immobilization, the ideal result being a solid ankylosis of the joint.

Except for incision and drainage, which are merely palliative, two types of corrective operative treatment have been employed, excision and arthrodesis. Steindler<sup>4</sup> recommended that arthrodesis be performed only when there is a chance of its working, that is, before there is too much melting down of tuberculous bone. He reserved resection for advanced conditions in which there is little expectation of obtaining a solid fusion. His best results were in his 5 cases of fusion.

Arthrodesis may be extra-articular, intra-articular or both. Putti<sup>5</sup> and Massart<sup>6</sup> have described the various technics in detail. The latter reported good results in 1 case fourteen months after the operation. In this case full thickness tibial grafts were used, together with small osteoperiosteal chips. Jones<sup>7</sup> recently described an extra-articular arthrodesis in which he angulated the acromion and implanted it in the humerus in the region of the greater tuberosity, thus securing ankylosis without actually encroaching on the diseased area. He obtained good functional and cosmetic results in 3 young adults followed eighteen months after operation. Curtis and Branch<sup>8</sup> employed the Jones technic in 2 children and found the operation well adapted for fusing a tuberculous joint in a child because it produces solid ankylosis without impairing the humeral epiphysis.

Codman<sup>9</sup> expressed the opinion that if a resection is undertaken radical excision of the articular head is preferable to excision of a localized area of diseased tissue. Richard and Courvoisier<sup>10</sup> advocated resection in preference to arthrodesis because the diseased focus is removed and the resulting function better. They reported 5 cases. Meyer-Burgdorff<sup>11</sup> did an arthroplasty of the shoulder in 8 cases and obtained good results. In cases of advanced disease in which more

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4. Steindler, A.: The Treatment of Tuberculosis of the Upper Extremity, *Southwestern Med.* **22**:168-171 (May) 1938.

5. Putti, V.: Artrodesi nella tubercolosi del ginocchio et della spalla, *Chir. d. org. di movimento* **18**:217-226 (Sept.) 1933.

6. Massart, R.: La tuberculose de l'épaule et l'artrodèse, *Rev. de chir., Paris* **68**:112-141, 1930.

7. Jones, R. W.: Extra-Articular Arthrodesis of the Shoulder, *J. Bone & Joint Surg.* **15**:862-871 (Oct.) 1933.

8. Curtis, F. E., and Branch, H. E.: Extra-Articular Arthrodesis of the Shoulder, *J. Bone & Joint Surg.* **19**:511-513 (April) 1937.

9. Codman, E. A.: The Shoulder, Boston, The Author, 1934, pp. 471-474.

10. Richard, A., and Courvoisier, J.: Indications et technique de la résection de l'épaule pour tumeur blanche, *Presse méd.* **41**:290-293 (Feb. 22) 1933.

11. Meyer-Burgdorff, H.: Die Resektion des Schultergelenkes bei Tuberkulose, *Arch. f. klin. Chir.* **175**:250-265, 1933.

conservative methods offer no hope, interscapulothoracic amputation of the arm can be done and a prosthetic appliance constructed for the patient. A case of such treatment was reported by Milch.<sup>12</sup>

Codman<sup>9</sup> pointed out that according to the present knowledge it is not possible to decide whether arthrodesis or excision is the superior operation. "We greatly need," he said, "a large collection of post-operative statistics to determine the relative value of these two operations." This paper represents a partial answer to that need.

The incidence of tuberculosis of the shoulder is probably less than 1 per cent of all cases of bone and joint tuberculosis. Sever<sup>13</sup> observed 17 cases in a study of 7,474 children with tuberculosis of the bones and joints. At the Lakeville State Sanatorium during the fourteen year period from 1926 to 1939 there were 24 cases of involvement of the shoulder among 1,076 admissions for tuberculosis of bones and joints, an incidence of 1.3 per cent. Of the 24 patients, 6 were female and 18 were male. The age on admission varied from 14 months to 57 years, with an average of 29 years. The age at onset of symptoms varied from 6 months to 49 years, with an average of 24 years. There were 5 cases of disease of the left shoulder and 19 cases of disease of the right. A follow-up study (largely by questionnaire) was obtained on every one of the 24 sanatorium patients included in this investigation.

Of the 24 patients studied, 12 underwent an arthrodesis (table 1); on 11 no operation was performed except occasional incision and drainage (table 2), and only 1 underwent excision of his shoulder joint. This last patient (J. C. C., fig. 1) was operated on at the Massachusetts General Hospital in 1919, and except for some limited motion he has "had no trouble since with the shoulder." He was treated at the Lakeville State Sanatorium primarily for tuberculosis of the hip, and a follow-up twenty-one years after his original operation revealed good function and no pain.

Of the 12 patients treated by arthrodesis, 4 were operated on at Lakeville, 6 at the Massachusetts General Hospital and 2 at the Newton Hospital. One of these (A. E. O.) is still hospitalized and has been followed for one year since operation. The remaining 11 were followed for three to thirteen years, or an average of seven years each, after operation. In every operative case the diagnosis of tuberculosis was confirmed pathologically. No patient required further operation or the continued use of any apparatus for support. At the time the follow-up study was made every patient reported some limitation of motion, but only 2 (E. W. B. and A. J. C.) complained of pain. Function of the shoulder was good

12. Milch, H.: Interscapulo-Thoracic Amputation for Secondarily Infected Tuberculosis of Shoulder, *Ann. Surg.* **97**:381-386 (March) 1933.

13. Sever, J. W.: Tuberculosis of the Shoulder in Children, *Boston M. & S. J.* **162**:383-386, 1910.

TABLE 1.—Patients Treated Operatively (by Arthrodesis)

Initials	Age at Onset of Symptoms	Age at Admission to Lakeville Sanatorium	Age at Operation	Sex	Side	Number of Sinuses on Admission	Tuberculosis of Other Organs	Place of Operation	Type of Operation	Years Followed Since Operation	End Results and Comment
M. W. B.	34	36	35	F	Right	3	0	Massachusetts General Hospital	Arthrodesis	11	Firm ankylosis; slight deformity; no sinuses; excellent function; working 5 years as book-keeper (see fig. 6)
E. W. B.	32	34	34	M	Right	1	0	Massachusetts General Hospital	Arthrodesis with graft	7	Occasional "arthritis" pain; fair function; no sinuses
M. O.	32	33	33	M	Right	0	Wrist	Massachusetts General Hospital	Arthrodesis with graft	7	Good function; no pain
A. I. O.	17	26	26	M	Right	3	Lungs	Massachusetts General Hospital	Arthrodesis	3	Discharged at own request, against advice; sinuses drain constantly; some pain when drainage stops; has not worked; further operation contemplated
M. DeS.	31	32	32	M	Right	0	Lungs	Lakeville State Sanatorium	Arthrodesis with graft	4	Has worked as paper hanger since discharge; good function; no pain; limited motion
A. K.	4	6	7	M	Right	2	0	Lakeville State Sanatorium	Arthrodesis with graft	10	Excellent function; no pain; limited abduction; no sinuses or drainage
S. N.	39	40	39	M	Left	0	0	Massachusetts General Hospital	Arthrodesis	4	Discharged at own request, against advice; wearing plaster shoulder spica, working now; no pain; good function
L. P.	6	7	8	M	Right	0	0	Lakeville State Sanatorium	Arthrodesis with graft	13	Works repairing watches; no pain; good function; general health good
E. E. S.	7	10	10	M	Right	0	0	Newton Hospital	Arthrodesis	6	Good function; no pain
W. B. T.	20	20	20	M	Right	0	Foot	Newton Hospital	Arthrodesis with graft	7	Discharged at own request, against advice; slight shoulder stiffness and limited motion; good function; no pain
S. V.	45	46	46	M	Left	0	0	Massachusetts General Hospital	Arthrodesis with graft	7	Works as janitor since discharge; firm ankylosis; no pain; good function
A. E. O.	17	19	21	F	Right	0	Hip, Spine, Wrist, Lungs	Lakeville State Sanatorium	Arthrodesis	1	Still hospitalized; good ankylosis; wears an airplane splint; no pain

TABLE 2.—*Patients Treated Without Operation*

Initials	Age at Onset of Symptom	Age on Admission to Lakeville State Sanatorium	Sex	Side	Number of Sinuses on Admission	Tuberculosis of Other Organs	Years Followed Since Discharge from Lakeville State Sanatorium	End Results and Comment
F. C.	49	57	M	Right	4	Spine	2	Discharged at own request, against advice; some pain; health falling; three sinuses still drain; weight loss 30 pounds (13.6 Kg.)
A. A. G.	17	29	F	Right	0	Foot, Wrist	5	Good function; slightly limited motion; health good; pregnant.
P. G.	41	42	M	Right	0	Lungs	6	Shoulder free from pain; good function; shoulder firmly ankylosed in 40 degree abduction (see fig. 4)
A. E. L.	39	41	M	Right	0	Spine, Testicle, Larynx, Lungs	1	Motion limited but free within limits; in sanatorium 6 months for pulmonary tuberculosis; required intubation for tuberculosis of larynx
J. J. L.	4	10	M	Right	0	Spine	3	Health fair; is able to play baseball; shoulder is ankylosed; good function
E. P.	23	25	F	Right	1	Spine	10	Able to work; no drainage; no reactivation of shoulder disease; good function; nephrectomy 5 years after discharge
A. S.	23	29	F	Right	2	Colon, Rectum	1	Died 3/28/33; shoulder disease spread; probably died from generalized tuberculosis
B. M. S.	25	27	F	Left	0	Chest, Tubes	1	Died 5/23/39; autopsy showed pulmonary tuberculosis and shoulder tuberculosis; thrombosis of left subclavicular and jugular veins; thoracoplasty 5/16/39
J. S. S.	8	24	M	Right	0	Kidneys, Hip	..	Died 12/2/38 of uremia and tuberculous nephritis; left nephrectomy on 2/14/34 and ureterostomy on 2/19/38
O. W.	39	41	M	Right	5	Glands, Hand	..	Died 2/15/34 of tuberculous shoulder; had downhill course; many sinus tracts (see fig. 3)
R. O.	½	1	M	Left	1	Chest	..	Hospitalized at Lakeville State Sanatorium past 6 years; wears plaster jacket with left shoulder splint; sinus not draining; no pain (see fig. 2)



or excellent in all but 1 (A. J. C.). He was the only patient too who continued to have draining sinuses, whereas 4 of the patients operated on had had draining sinuses on admission. Since the operations were done by different surgeons, there was no uniformity of technic. For 7 of the 12 patients, however, tibial or osteoperiosteal grafts were employed. It is interesting to note that only 5 of the 12 operatively treated patients had tuberculous involvement of other organs, whereas every one of the patients not operated on had multiple tuberculous foci.

Eleven patients were not operated on except for an occasional incision and drainage. In the cases of only 3 of this group was the diagnosis made pathologically; the condition of the remainder was

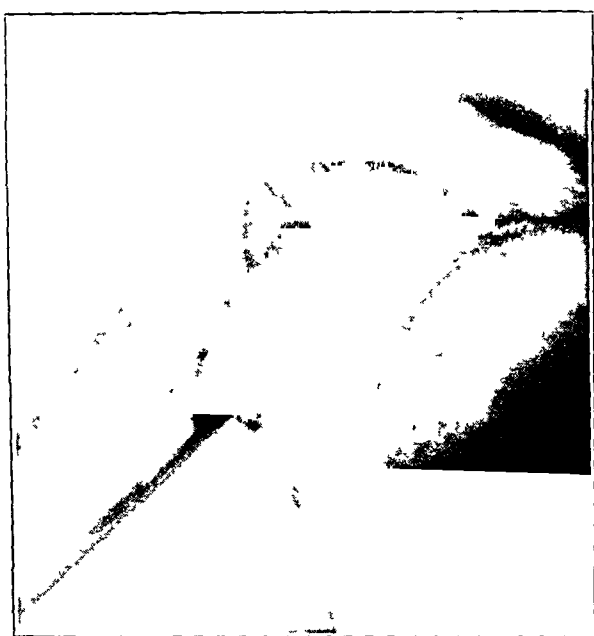


Fig. 1.—Left shoulder of J. C. C. seventeen years after excision. The patient reports good function and no pain.

diagnosed clinically and roentgenologically. One of the patients (R. C., fig. 2) is still in the hospital. Two patients died while in the sanatorium, 1 (J. S. S.) of uremia and tuberculous nephritis and the other of tuberculosis of the shoulder. The latter, a Chinese cook (C. W., fig. 3) had five draining sinuses and extensive involvement of his cervical glands. Two additional patients died about one year after discharge from the sanatorium, 1 (B. M. S.) of pulmonary tuberculosis and tuberculosis of the shoulder and the other of generalized tuberculosis. The latter (A. S) had been suffering from tuberculosis of the colon, rectum and peritoneum, and it appeared as if her shoulder disease had spread to involve the chest wall and the other shoulder as well.



Fig. 2.—*A*, tuberculosis of the left shoulder in R. C., a 14 month old infant. There were drainage from one sinus and considerable pain. *B*, condition six years later. Note the development of the humeral head and the "squaring" of the epiphysis. The shoulder is still partly immobilized. There is no pain. The response to conservative treatment is favorable.

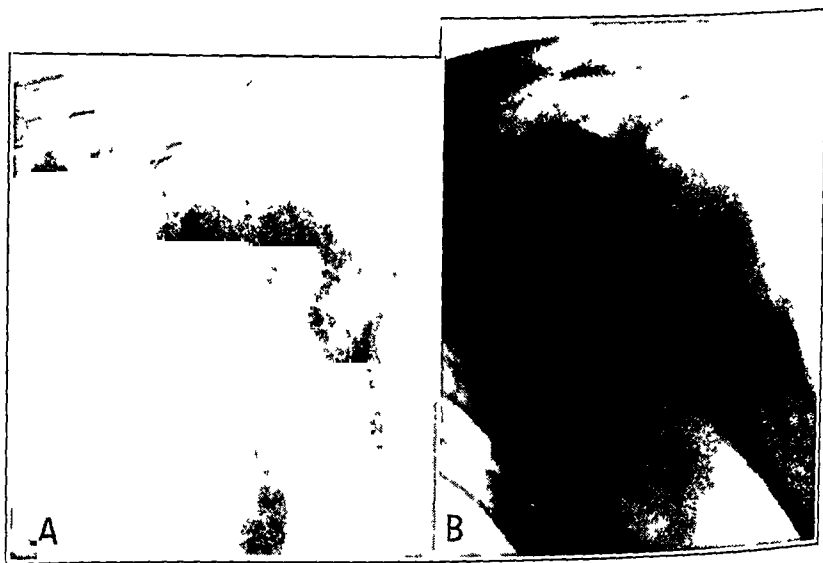


Fig. 3.—*A*, tuberculosis of the right shoulder in patient C. W. There is extensive destruction of the head of the humerus and the glenoid fossa. *B*, condition one year later; note the marked extension of the disease. The patient died. Operation in the presence of such a fulminating process would have been futile.



Fig 4—Tuberculosis of the right shoulder of patient P. G. Solid ankylosis was obtained in a nonoperative case. Good function is reported. Such firm bony union without operation is unusual.



Fig. 5.—*A*, right shoulder of M. W. B. two years after arthrodesis. *B*, same shoulder nine years later; note the atrophy of the scapula and the maintenance of the scapulohumeral angle. The functional result is excellent.

The 6 remaining patients have been followed for one to ten years since discharge, an average of four years each. One (F.C) has lost weight and has three draining sinuses. Two others have only fair function, and the remaining 3 have good function and have shown no reactivation of the process.

#### CONCLUSIONS

The treatment of tuberculosis of the shoulder should consist of a period of sanatorium care followed by operation. Whether arthrodesis or excision should be performed is still an unsettled question, because the available statistics are too few to be decisive. Arthrodesis is a valuable operation. The 12 patients mentioned here on whom this operation was performed were followed for an average of seven years postoperatively and reported consistently good results. A single case in which an excision was done was followed for twenty-one years after operation, and the result in this isolated case is good. A period of observation before operation is important because it aids in evaluating the course of the tuberculous process and gives the patient an opportunity to improve his general condition. Needless to say, it is futile to operate in the presence of a rapidly fulminating disease or of marked toxicity from multiple tuberculous foci. With children, conservative treatment yields good results, but a well planned extra-articular fusion may shorten the duration of the illness and period of hospital care.

#### SUMMARY

The end results in 24 cases of tuberculosis of the shoulder are reported.

In 12 cases in which an arthrodesis was done the functional results were uniformly good.

In 11 cases no operation was performed; only 3 of the patients in this group reported good function of the shoulder.

In 1 case in which excision was done a functionally good shoulder was reported twenty-one years after operation.

# RELATION OF THE SCALENUS ANTICUS MUSCLE TO PAIN IN THE SHOULDER

## DIAGNOSTIC AND THERAPEUTIC VALUE OF PROCAINE INFILTRATION

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Pain in the region of the shoulder and arm is a frequent diagnostic and therapeutic problem. Such pain has often been attributed to some form of subacromial bursitis, of traumatic origin, of the chronic type with adhesions or of the acute or chronic type due to calcified deposits in the supraspinatus tendon, although the evidence in favor of the diagnosis was in many instances unconvincing. It was always difficult to understand the radiation of pain to the neck and down the arm as due to a bursal lesion, but Codman's observations so exactly fit the clinical picture that I was inclined to accept his explanation of a "pseudoneuritis." Codman,<sup>1</sup> in writing on calcified deposits in the supraspinatus tendon, said: "If there has been a long, painful stage all the adjoining nerves become sensitized and the phenomena we call 'neuritis' supervene." . . . "The pain or hyperesthesia, originally mainly felt in the circumflex distribution about the shoulder and near the insertion of the deltoid halfway down the arm, becomes more diffused. It shoots up into the neck, onto the back of the shoulder blade and down the distribution of the radial nerve to the thumb and forefinger. Even the ulnar and median nerves may become sensitized, the hand and fingers swell, and the skin over them becomes glossy. The picture is that of 'brachial neuritis' but removal of the calcified deposit relieves it."

The explanation of the phenomena observed in the hand and arm as due to a sensitization of adjoining nerves was difficult to follow, and in recent years I have become more and more impressed with the similarity of the clinical findings to those of the scalenus anticus syndrome. It has become apparent that pain in the shoulder produces spasm and contracture of the muscles of the shoulder girdle, in which the scalenus

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1. Codman, E. A.: The Shoulder, Boston, The Author, 1934.

anticus often takes part, and thus a "secondary" scalenus anticus syndrome supervenes. That this is true may be proved by the prompt relief of the secondary symptoms by injection of procaine hydrochloride into the scalenus anticus muscle.

In the recent literature attention has also been focused on the role of the sympathetic nervous system in producing pain. There is no question that the pain of sprains and articular fractures may be relieved by local infiltration,<sup>2</sup> and there is evidence to indicate that block of the sympathetic fibers which supply an injured area produces a similar effect.<sup>3</sup> Block of the lumbar sympathetic fibers has been used by Ochsner and DeBakey<sup>4</sup> for relief of the pain and vascular stasis associated with thrombophlebitis. This newer concept of the origin of some types of pain I believe must be taken into account in considering pain in the region of the shoulder and I have some evidence to indicate that disturbance of the sympathetic nervous system has a part in the production of pain in this area.

#### THE SCALENUS ANTICUS SYNDROME

That the scalenus anticus muscle is a factor in producing the mechanical neuritis of the brachial plexus sometimes associated with a cervical rib has been known since 1906,<sup>5</sup> and section of the muscle for the relief of symptoms has been performed many times with good results, with or without removal of the cervical rib itself. There have been, however, a number of instances in which a typical cervical rib syndrome presented itself but in which no cervical rib could be demonstrated. Naffziger, in a personal communication to Ochsner, Gage and DeBakey,<sup>6</sup> described 2 cases in which relief was obtained by sectioning the scalenus anticus muscle. The latter authors reported 4 cases in which relief was obtained after such section and cited a report by Carroll of a similar successful operation. Since then the operation has been performed many times.

#### MECHANISM

The scalenus anticus muscle has its origin from the transverse processes of the third to the sixth cervical vertebra and its insertion into the scalene tubercle on the upper surface of the first rib, close to

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2. Cullumbine, H.: Treatment of Fractures by Local Anaesthesia, *Lancet* 2:552-553 (Sept. 2) 1939.

3. Campbell, W. G.: Role of Sympathetic Nervous System in Segmental Pain, *Lancet* 2:930-932 (Oct. 28) 1939.

4. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocain Block of Sympathetics, *Surgery* 5:491-497 (April) 1939.

5. Naffziger, H. C., and Grant, W. T.: Neuritis of the Brachial Plexus Mechanical in Origin, *Surg., Gynec. & Obst.* 67:722-730 (Dec.) 1938.

6. Ochsner, A.; Gage, M., and DeBakey, M.: Scalenus Anticus (Naffziger) Syndrome, *Am. J. Surg.* 3:669-693 (June) 1935.

the sternum. The brachial plexus and the subclavian artery lie behind the lower portion of the muscle and on the other scalenus muscles, in a triangular space made by the first rib below and the converging muscles above. There are sympathetic fibers lying on the under surface of the inner cord of the brachial plexus and on the prevertebral muscle mass.

Spasm, increased tension or unusual hypertrophy of the scalenus anticus muscle may cause direct pressure on the brachial plexus or may cause indirect pressure by elevating the first rib unduly, the elevated rib pressing into the brachial plexus and the subclavian artery as they arch over it to go down the arm. In addition, since the scalenus anticus muscle is supplied by branches of the lower four cervical nerves, which form the brachial plexus, irritation of the plexus is thought to cause further scalenus spasm with increased pressure on the plexus and further elevation of the first rib, establishing a vicious cycle.<sup>6</sup>

When the shoulder girdle droops, the first rib becomes relatively higher than normal, and patients with droopy shoulders are more likely to exhibit symptoms. This is borne out clinically.

This mechanical neuritis of the brachial plexus, with or without associated vascular disturbances, is manifested commonly by pain about the shoulder; however, the pain may be located anywhere from the neck to the fingers. It is occasionally accompanied with tingling and numbness along the inner side of the arm, along the forearm and in the fourth and fifth fingers. Vascular disturbances may be present, such as diminished or absent radial pulse, coldness and cyanosis of the arm and hand.

#### ETIOLOGY

Naffziger and Grant<sup>5</sup> have pointed out that the relative position of the shoulder is high in infants and children and that a gradual descent occurs to the adult position; in the female the descent is greater and the ultimate position of the shoulder is more sloping. He suggested also that the loss of muscular tone and the drooping of the shoulders seen in the aged may be additional factors.

The inciting cause of the syndrome has so far not been clear. The majority of patients have given a history of some minor injury to the shoulder, so that possibly a sprain of the scalenus anticus muscle may have occurred. In the cases of others who recalled no injury, it has been assumed that the progressive dropping of the shoulder with advancing years was the only factor. In 1938 Freiberg<sup>7</sup> expressed the opinion that spasm of the scalenus anticus muscle might be a complication of many common lesions about the shoulder girdle, such as calcification

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7. Freiberg, J. A.: The Scalenus Anterior Muscle in Relation to Shoulder and Arm Pain, *J. Bone & Joint Surg.* 4:860-869 (Oct.) 1938.

of the supraspinatus tendon, arthritis of the shoulder or arthritis of the cervical portion of the spine, and Bishop,<sup>8</sup> of the same clinic, in 1939 described in detail 1 of 11 cases of "a rather typical scalenus anticus syndrome in which the condition was entirely relieved by treatment of the calcification of the supraspinatus tendon." I hope to demonstrate that any painful lesion about the shoulder may excite spasm of the scalenus anticus muscle with its characteristic train of symptoms.

#### DIAGNOSIS

Ochsner, Gage and DeBakey tried to differentiate the scalenus anticus syndrome from similar clinical conditions, such as cervical rib, subacromial bursitis, rupture of the supraspinatus tendon, cervicodorsal sympathalgia, Raynaud's disease and brachial neuritis. If, however, spasm of the scalenus anticus muscle may be a complication of any of these conditions, it becomes important to evaluate the part of the primary condition and the part of the spasm rather than to insist on a differential diagnosis. These authors based the diagnosis of scalenus syndrome on (a) persistent localized tenderness over the scalenus anticus muscle in the supraclavicular space, with radiation of pain into the arm, and (b) vascular changes, "consisting of diminution in, and at times complete absence of the radial pulse produced by rotating the head toward the affected side and extending the chin," and oscillometrograms showing a definite decrease in the index on the affected side, both thought to be due to pressure on the subclavian artery.

Theis<sup>9</sup> studied these diagnostic criteria and came to these conclusions: 1. Since more than 50 per cent of the conditions diagnosed as scalenus anticus syndrome are associated with a history of trauma to the neck or shoulder, the tenderness and the aggravation of the peripheral pain by digital pressure could occur with traumatic neuritis or any type of neuritis.

2. Reduction or obliteration of the peripheral pulse on deep inspiration with the scalenus anticus muscle on tension (head turned to the affected side and hyperextended) occurs in most normal persons. Normal subjects often exhibit an increased oscillometric index on changing from the sitting to the recumbent position, although the increases exhibited by patients suspected of having the scalenus anticus syndrome are frequently greater. It would therefore appear that only limited significance may be attached to local signs and vascular disturbances unless they are striking.

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8. Bishop, W. A.: Calcification of the Supraspinatus Tendon, *Arch. Surg.* 39:231-246 (Aug.) 1939.

9. Theis, F. V.: Scalenus Anticus Syndrome and Cervical Ribs, *Surgery* 6:112-125 (July) 1939.



Gage,<sup>10</sup> in April 1939, suggested that one might get temporary relief of the scalenus spasm by injecting procaine hydrochloride into the muscle and that this would be of importance in identifying the syndrome. He gave injections to 2 patients with the scalenus anticus syndrome, with relief of symptoms for eight hours and four hours, respectively. He gave an injection also to a patient with a cervical rib with temporary complete relief of symptoms. He performed the diagnostic test as follows: "With the patient in the recumbent position, the head is turned toward the unaffected side. The scalenus anticus muscle is palpated behind and lateral to the sterno-mastoid muscle. With the index finger of the left hand palpating the lateral border of the scalenus anticus muscle, a needle is inserted into its lateral edge. The muscle is then infiltrated with 1 per cent novocain through its lower half, care being taken not to infiltrate the phrenic nerve or brachial plexus. Within five to ten minutes the scalenus anticus muscle is completely relaxed and the patient is temporarily relieved of symptoms."

This seemed to be a simple method of determining the influence of the scalenus anticus muscle on the symptoms accompanying painful lesions of the shoulder of known or unknown cause. This procedure was carried out on 40 consecutive patients complaining of pain about the shoulder. The injections were made with the patient in the sitting position, about 10 cc. of 1 per cent procaine hydrochloride solution being used in most instances. A total of 78 injections was given. Usually the needle was pointed almost directly posteriorly, toward the transverse processes. Often contact with the processes was made, and the needle was then withdrawn slightly before the injection was started.

#### PHENOMENA OBSERVED AFTER INJECTION

The palpable thickness of the scalenus anticus muscle mass was variable, and in order to be certain of infiltrating the muscle thoroughly the needle was carried down close to the transverse processes of the cervical vertebrae, many times touching them. Before injection and several times during injection the plunger of the syringe was drawn back to determine whether the point of the needle was in a blood vessel. When blood was drawn the position of the needle was changed slightly. Relief of pain, when it occurred, usually began within two to five minutes, and the maximum effect was observed within ten to twenty minutes. Shortly after the relief of pain began, there were noticed in most cases redness and lacrimation of the eye on the side of injection, accompanied with enophthalmos, drooping of the eyelid and constriction of the pupil. The redness was due to intense dilatation of the subconjunctival vessels. In many instances the hand became warmer, flushed

10. Gage, M.: Scalenus Anticus Syndrome, *Surgery* 5:599-601 (April) 1939.

and slightly larger than the one on the opposite side. These ocular and peripheral vascular phenomena were due to paralysis of the cervical sympathetic fibers and as a rule disappeared within forty-five to ninety minutes. Evidence of anesthesia of the brachial plexus was seen in only



The upper photograph was taken immediately after the injection and before withdrawal of the needle. The superimposed diagram shows the approximate relation of the important structures: *B*, brachial plexus (rather high); *A*, subclavian artery; *S*, insertion of the scalenus anticus muscle into the first rib; *M*, the sternal and clavicular heads of the sternocleidomastoid muscle. The lower photograph shows the drooping eyelid and enophthalmos after injection.

a few instances, consisting of some numbness in the fingers. In 1 instance there was numbness in the supraclavicular space. Occasionally the patient complained of slight giddiness, nausea and faintness, but in

no instance were these severe enough to cause concern. In 2 or 3 instances slight puffiness and discoloration at the base of the neck occurred, due to leakage from a perforated vein. Slight hoarseness was present in 2 or 3 patients after injection, and this disappeared in an hour or two. From 1 patient chyle was aspirated, probably from the thoracic duct at the point where it lies on the subclavian vein. No disturbance followed. No other untoward effects were observed.

#### CLASSIFICATION OF CONDITIONS

On reviewing the records I found that 34 of the patients could be classified into a few main groups, not always mutually exclusive, a point to be considered later. In 6 instances either the findings were inconclusive or the records were incomplete. The groups are as follows:

- |   |    |
|---|----|
| 1. Scalenus syndrome.....                         | 10 |
| 2. Scalenus syndrome following trauma.....        | 6  |
| 3. Subacromial bursitis with adhesions.....       | 12 |
| 4. Calcification in the supraspinatus tendon..... | 3  |
| 5. Other conditions about the shoulder.....       | 3  |

1. *Scalenus Anticus Syndrome*.—The 10 cases placed in this group were characterized by the onset of pain in the brachial distribution without a history of antecedent trauma and by the absence of signs of subacromial bursitis or any other identifiable lesion of the neck or shoulder girdle. In 4 cases the symptoms were bilateral. Roentgen examination of the shoulder and of the cervical portion of the spine was indicated in about half of the cases and gave negative results in all but 1, in which there were unusually long transverse processes of the seventh cervical vertebra. Definite tenderness of the scalenus anticus muscle mass was present in 7 of the 14 shoulders.

The distribution of pain was variable, but in 7 of the 10 cases it was that distribution which is usually taken to characterize brachial neuritis—pain over the neck and shoulder radiating to the elbow or to the wrist and fingers. Pain over the scapula and the upper part of the chest may accompany the pain in the shoulder and arm or may be present without it.

The character of the pain varied considerably. It was described as dull, constant and nagging in some instances, as sharp and lancinating in others and in single cases as burning pain, a sense of tightness and a sensation as of pins and needles.

The duration of symptoms was less than two months in 2 cases and two months or over in 8 cases. As a rule the pain had become progressively worse from the time of onset to the time of the patient's admission to the hospital.

TABLE 1.—*Scalenus Syndrome*

Patient	Sex	Age	Duration of Symptoms	Distribution of Pain	Physical Findings	Progress	
						Result of Scalenus Injection	Did not return
1. A. McC.	F	51	6 months	Dull over right scapula; occasional numbness right hand Burning pain right breast; sharp pain right shoulder, neck, scapula, ribs, breast and down arm	Slight limitation of elevation and slight tenderness of right scalenus Tenderness over shoulder, right scalenus and trapezius; some spasm and limitation of elevation; lump in right breast	6/12/39: Pain improved; motion easier; hand became numb 6/12/39: Pain very much relieved	6/10/39: Lump in breast excised for chronic cystic mastitis; 7/1/39: felt fine, discharged; 10/21/39: (follow-up) slight pain right breast and occasional slight stiffness of right arm 10/21/39: Complained of stiff neck and recurrence of pain
2. F. V.	F	36	2 months	Outer side of left breast	Left scalenus tender; pressure on it caused pain in breast Tender over scapula distal to right acromion (lipoma removed 2 years before)	10/21/39 Pain relieved	5/29/39: Complained of occasional pain on top of shoulder and slight pain in index finger; scalenus re-injection; 5/31/39: injection into painful scar; 7/24/39: slight recurrence, scalenus injection; 10/23/39: (follow-up) shoulder pain much improved; pain in hand and fingers completely gone 9/1/39: No statement of recurrence; postural exercises prescribed
3. M. C.	F	36	3 months	Right side of neck; right deltoid, to elbow, wrist and fingers mainly index	Shoulder tender, pain when scalenus made tense No abnormalities	8/25/39: Fair relief of pain	Onset in hospital while recovering from operation for gastric carcinoma; no recurrence by 12/21/39 (discharged) 12/22/39: Pain in right shoulder and neck definitely improved since pain in right arm absent since injection, 12/23/39: no recurrence of pain in arms; precordial pain less
4. H. M. B.	M	34	2 months	Crampy; right shoulder, neck, between shoulders, along arm Dull, constant, nagging, both shoulders, referred to insertion of deltoid	Old rheumatic heart disease; tender over insertion of right scalenus anticus; transverse processes of 70 vertebra unusually long on roentgen examination	11/10/39: Right side, immediate relief; 11/11/39: left side, immediate relief 12/19/39: Right side, no pain immediately prior to injection; scalenus injected and right 5-6 7 foot injection; 12/22/39: left side, pain in upper left side of chest prior to injection; disappeared to injection; 2/10/40: Left side, complete relief in 10 minutes; arm felt heavy	2/13/40: Recurrence; left reinjection, with complete immediate relief; complained of substernal oppression; no further injections
5. M. K.	M	66	11 days	Left, slight, upper part of chest, shoulder and arm Right, severe, neck, shoulder, down arm	Left scalenus more tender than right; pressure caused pain down arm; tender over head of left humerus	1/12/40: Complete relief of pain; some numbness in suprascapular space 1/13/40: Complete relief for several hours	4/19/40: Pain in arm gone; still some pain in shoulder; 4/30/40: recurrence; injected 6 cc. procaine hydrochloride and 10 cc. saline; pain disappeared Reinjection 4 times with complete relief for a few hours each time Reinjection of alcohol injection, with slight relief Pain returned within 1 1/2 hours; 4/25/40: pain returned; 4/27/40: pain returned; 4/28/40: pain returned
6. A. B.	F	41	Left, 6 months Right, 5 months	Left, tightness, numbness and occasional pins and needles sensation in whole shoulder, arm and side of chest; right, upper arm to hand; similar Dull; right, neck and shoulder to wrist	Negative	1/12/40: Complete relief of pain; some numbness in suprascapular space 1/13/40: Complete relief for several hours	4/19/40: Pain in arm gone; still some pain in shoulder; 4/30/40: recurrence; injected 6 cc. procaine hydrochloride and 10 cc. saline; pain disappeared Reinjection 4 times with complete relief for a few hours each time Reinjection of alcohol injection, with slight relief Pain returned within 1 1/2 hours; 4/25/40: pain returned; 4/27/40: pain returned; 4/28/40: pain returned
7. J. Do	F	40	2 months	Severe, right neck radiating to middle of jaw, occiput and back of shoulder Over shoulder radiating to arm, forearm and hand	Aneurysm aorta and innominate; Horner's syndrome, atrophy of central nervous system Right scalenus tender; over shoulder it is quite prominent	1/12/40: Complete relief of pain; some numbness in suprascapular space 1/13/40: Complete relief for several hours	4/19/40: Pain in arm gone; still some pain in shoulder; 4/30/40: recurrence; injected 6 cc. procaine hydrochloride and 10 cc. saline; pain disappeared Reinjection 4 times with complete relief for a few hours each time Reinjection of alcohol injection, with slight relief Pain returned within 1 1/2 hours; 4/25/40: pain returned; 4/27/40: pain returned; 4/28/40: pain returned
8. B. B.	F	22	3 weeks	Severe, right neck radiating to middle of jaw, occiput and back of shoulder Over shoulder radiating to arm, forearm and hand	Aneurysm aorta and innominate; Horner's syndrome, atrophy of central nervous system Right scalenus tender; over shoulder it is quite prominent	1/12/40: Complete relief of pain; some numbness in suprascapular space 1/13/40: Complete relief for several hours	4/19/40: Pain in arm gone; still some pain in shoulder; 4/30/40: recurrence; injected 6 cc. procaine hydrochloride and 10 cc. saline; pain disappeared Reinjection 4 times with complete relief for a few hours each time Reinjection of alcohol injection, with slight relief Pain returned within 1 1/2 hours; 4/25/40: pain returned; 4/27/40: pain returned; 4/28/40: pain returned
9. M.	M	55	5 months	Severe, right neck radiating to middle of jaw, occiput and back of shoulder Over shoulder radiating to arm, forearm and hand	Aneurysm aorta and innominate; Horner's syndrome, atrophy of central nervous system Right scalenus tender; over shoulder it is quite prominent	1/12/40: Complete relief of pain; some numbness in suprascapular space 1/13/40: Complete relief for several hours	4/19/40: Pain in arm gone; still some pain in shoulder; 4/30/40: recurrence; injected 6 cc. procaine hydrochloride and 10 cc. saline; pain disappeared Reinjection 4 times with complete relief for a few hours each time Reinjection of alcohol injection, with slight relief Pain returned within 1 1/2 hours; 4/25/40: pain returned; 4/27/40: pain returned; 4/28/40: pain returned
10. W. W.	F	1	2 months	Severe, right neck radiating to middle of jaw, occiput and back of shoulder Over shoulder radiating to arm, forearm and hand	Aneurysm aorta and innominate; Horner's syndrome, atrophy of central nervous system Right scalenus tender; over shoulder it is quite prominent	1/12/40: Complete relief of pain; some numbness in suprascapular space 1/13/40: Complete relief for several hours	4/19/40: Pain in arm gone; still some pain in shoulder; 4/30/40: recurrence; injected 6 cc. procaine hydrochloride and 10 cc. saline; pain disappeared Reinjection 4 times with complete relief for a few hours each time Reinjection of alcohol injection, with slight relief Pain returned within 1 1/2 hours; 4/25/40: pain returned; 4/27/40: pain returned; 4/28/40: pain returned

TABLE 2.—*Scalenus Anticus Syndrome Following Trauma*

Patient	Sex, Age	Date and Kind of Injury	Onset and Distribution of Pain	Physical Findings	Result of Scalenus Injection	Progress
1. E. W.	F, 60	12/14/39: Fell on face on pavement	Immediately after fall, then progressively worse; top of shoulder, radiating to elbow	Trapezius very tender, infraclavicular space tender	12/21/39: Immediate relief of all pain except in a small area behind middle of clavicle	12/22/39: Had first good night's sleep in a week; a little persistent pain over side of neck, insertion of deltoid and spine of scapula; reinjection, slight pain over spine of scapula remained
2. M. F.	F, 57	8/31/39: Lifted a baby abruptly; had noted paresthesias in left index and middle fingers for 2 years	Immediate; became worse, more at night, unable to sleep; top of left shoulder, deltoid, down medial side of arm	Motion painful; left scalenus very tender; transverse processes of 7th cervical vertebra unusually long on roentgen examination	9/16/39: Marked immediate relief; no effect on paresthesias of fingers	Relief for 2 days; reinjection 9/19/39; relief for 3-4 days; reinjection 9/28/40; 10/17/39 (follow-up), slight pain; reinjection, 4/27/40, still some mild pain
3. A. P.	F, 54	1/15/40: Automobile accident	Immediate; severe, sharp; left side neck and left shoulder, radiating to elbow	Left scalenus and cervical transverse processes tender; tension on scalenus caused pain over shoulder, radiating down arm	1/32/40: Immediate but not complete relief of pain	Patient returned later; physical therapy given
4. J. P. M.	M, 40	1/15/40: Blow on left shoulder	Constant, aching, more severe anterior aspect left shoulder; radiating to neck and down arm to elbow	Tender over anterior aspect of left shoulder and over left scalenus; marked limitation of shoulder motion	1/19/40: Immediate relief of pain and muscle spasm; range of motion increased	Severe pain returned in 2 hours and lasted 2 hours; mild pain after 12 hours; no pain when examined on 1/20/40; 1/25/40, only slight pain at base of neck
5. J. B.	M, 36	11:30 p.m., 1/25/40: Fell downstairs and landed on right shoulder	Onset 6 a.m. 1/26/40: sharp pain in right shoulder, radiating up neck	Exquisite tenderness over acromion and trapezius, abduction of arm 40 degrees	1/26/40, 12 noon: Complete relief of pain at rest and only slight pain on motion; range of motion improved	1/27/40: Almost complete relief of pain and almost full range of motion; heat and methyl salicylate advised; 1/30/40, no pain; slight limitation of motion
6. H. S.	F, 40	4/1/40: Fell down steps and struck left shoulder	Steady aching pain over upper margin left scapula and lower portion of trapezius	Pain on full elevation of arm; left scalenus tender	4/9/39: About three fourths of pain disappeared; hand and arm became slightly numb	4/11/40: Complete relief of all pain and full range of motion

TABLE 3.—*Subacromial Bursitis with Adhesions*

Patient	Sex, Age	History	Distribution of Pain	Effect of Scalenus Injection	Progress
1 A Z	F, 68	Severe pain and restricted motion for 3 months; onset 1 month after a fall; treated by manipulation under anesthesia 5/12/39, followed by exercises; motion greatly improved, but pain persisted	Left shoulder, radiating over back and down arm to elbow	5/26/39. Immediate marked relief of pain	No recurrence by 7/7/39, when last seen
2 I T	F, 65	Severe pain and restricted motion for 1 year after straining shoulder, occasional prickly sensation in fingers, manipulation 3/6/39, followed by exercises, motion improved, but pain persisted	Right shoulder, base and back of neck	5/23/39. Immediate marked relief of pain	6/11/39. No recurrence, but pectorals major was found tense and tender, procaine and saline solution injected; recurrence of pain 10/30/39, with occasional numbness in right 3d and 5th fingers, three additional injections by 2/12/40; last seen 3/1/40, pain slight, persistent myositis of pectoralis major (mild)
3 M L	F, 54	Severe pain and restricted motion following a strain of the shoulder 3 months before, occasional prickly sensation in fingers; manipulation 3/6/39, returned 10/17/39, little improved, having performed no exercises	Left shoulder, radiating down arm to fingers, which were cold, dusky and stiff	10/17/39. Immediate relief of pain; hand became warm, pink and less stiff	10/24/40. Partial recurrence of pain and visomotor disturbance; had not been exercising, advised hospitalization; patient declined
4 C S	F, 61	Severe pain and restricted motion following a blow on the back of the shoulder 7 months before	Left shoulder down arm to wrist	12/8/39. Distinct relief of pain	Brachial plexus block anesthesia induced immediately after scalenus injection and manipulation; clavicle fractured, 12/9/39, pain at fracture site, no pain in shoulder or arm; 1/24/40, free of pain, range of motion much improved, discharged
5 A T	F, 44	Dull aching pain in right shoulder since automobile accident 9/13/40, fracture of both bones in right forearm, motion became restricted	Right shoulder, anterior, superior and posterior aspects	11/27/39. Immediate complete relief and increased range of motion	Relief lasted 2 or 3 days, then return of pain not so severe as before, exercises prescribed; 12/16/39, reanjection; no pain immediately before injection, range of motion improved
6 I S	F, 51	Fracture of right humerus 10/7/39, stiff shoulder 11/11/39, 11/16/39, complaint of shoulder pain	Right acromioclavicular joint, radiating to insertion of deltoid	12/28/39. Pain over deltoid disappeared, but pain at acromioclavicular joint unimproved, pain on motion disappeared	Exercises prescribed, at a later visit pain was relieved and mobility much improved

7. A. K.	M, 53	While in bed recovering from an operation for peptic ulcer, began to have pain and restricted motion in both arms (5-6 weeks before); severe on right, mild on left	Right, top of shoulder down to 4th and 5th fingers; left, pain from deltoid to elbow	Right: 1/5/40, relief of pain and increased range of motion; left: 3/24/40, complete relief and increased mobility	1/6/40: Still improved; 1/8/40, injection; 1/11/40, manipulation; 1/18/40, recurrent severe pain, reinjection; 1/23/40, reinjection with relief for 2 days; recurrence; roentgen treatment, without relief; 2/24/40, pain still troublesome but not so severe
8. M. C. B.	F, 56	Progressively increasing pain and decreasing mobility, both shoulders, for 13 months; pain severe	Top of right shoulder, radiating to elbow; top of left shoulder, radiating to wrist	3/19/40: Right scalenus, little pain prior to injection	3/26/40: Stated that pain was less for 36 hours and then returned; admitted to hospital for traction in abduction, after which mobility increased; 4/23/40, left scalenus injection, pain diminished, mobility increased for 2 days; 4/30/40, right scalenus injection, mobility increased; patient much improved since admission
9. A. N.	F, 65	3/4/40: Fracture of right radius; 3/15/40, complained of soreness in left shoulder progressively worse since fall on shoulder 6 weeks before; 3/15/40, injection in tender area just lateral to coracoid, with relief of pain for 2 days; pain recurred; reinjection in this area on 2/19/40 with temporary relief	Left shoulder, soreness radiating to elbow; drawing and aching pain	4/12/40: No pain immediately prior to injection	4/15/40: Patient stated she had much more relief from the scalenus injection than from the other injections
10. D. R.	F, 62	12/16/39: Dull pain in right shoulder and inability to elevate arm following fall on hand 12/15/39; impacted fracture of head of humerus on roentgen examination	Right shoulder	12/16/39: No effect	
11. M. G.	F, 51	3/15/40: Complained of progressively increasing pain and decreasing mobility in right shoulder	Right shoulder, radiating to forearm	3/15/40: Relief of pain and increased mobility	7/10 recurrence of pain by 3/4/40, when she was sent to physical therapy department because of swelling and occasional numbness in right hand; 4/13/40 (follow-up), felt fine except for occasional slight pain
12. F. W.	M, 60	Pain and restricted motion following a fall down stairs 2 months before; occasional numbness of fingers and swelling of hand	Top and back of right shoulder, radiating to fingers	2/21/40: Complete relief of pain, increased mobility	No recurrence of pain by 4/9/40; shoulder manipulated under divinyl oxide, followed by pain from neck to wrist; scalenus injection, partial relief; 4/15/40: Still severe pain and restricted motion; injections in scalenus and subacromial bursa, and arm manipulated; 4/18/40, pain in bone, motion not improved; 4/29/40, pain only on motion, mobility much improved

The first injection of procaine hydrochloride into the scalenus muscle mass gave uniform and striking effects in these cases. In 13 shoulders there was either immediate complete relief of pain (8 cases) or marked amelioration (5 cases). In 1 shoulder there was little or no pain immediately prior to injection and hence no immediate change, but the customary pain which appeared afterward was much lessened.

The most surprising effect was the duration of relief. In several instances the pain failed to return. In others the relief lasted for many days and the recurrence was notably milder than the original pain. When this therapeutic effect became evident I was encouraged to repeat the injections in order to obtain permanent relief if possible. Four shoulders are known to be completely well or much improved, and 3 shoulders are improved and are still being treated. Seven patients have not returned for additional treatment, nor have I been able to obtain data on them by correspondence.

2. *Scalenus Anticus Syndrome Following Trauma.*—I have included in this group 6 cases in which the patients complained of pain about the shoulder following an injury, such as a fall, a blow or a strain. The duration of symptoms was six hours in 1 case and from four to sixteen days in 5 cases. The pain was a dull constant ache in some cases and was sharp and severe in the others. The pain was over the shoulder with radiation down the arm in 4 cases and over the shoulder and the side of the neck in 2 cases.

The physical signs in some cases were those of an acute soft tissue injury—tenderness over the scalenus and trapezius muscles and restriction of motion due to pain and muscle spasm. The signs in 1 patient suggested acute traumatic subacromial bursitis. In some the signs were meager, consisting only of tenderness over the scalenus muscles.

The first injection into the scalenus muscles gave immediate and complete or almost complete relief of pain in all cases, which lasted for one or more days. In 4 cases no additional injections were required. The recurrence in 1 patient was very mild and in the other was as severe as the original pain. This patient showed unusually long transverse processes of the seventh cervical vertebra, and she received additional injections, with considerable lasting relief.

An effect which I did not at first appreciate and record was the increased range of shoulder motion which followed injection. This was striking in several of the patients.

3. *Subacromial Bursitis with Adhesions.*—In this group I have placed the cases of 12 patients who complained of progressively increasing pain about the shoulder and who exhibited marked restriction of motion at the shoulder due to adhesions in the subacromial bursa. In 9 of these cases there was a history of trauma to the shoulder. The



symptoms were bilateral in 2 patients. The distribution of pain in 10 instances was over the shoulder, radiating down the arm, elbow, wrist or hand. In 3 instances the pain was limited to the shoulder and the base of the neck, and in 1 instance it was in the area extending from the deltoid to the elbow. In most patients the pain was extremely severe. It was often dull and aching but sometimes sharp, and it was intensely aggravated by motion, especially attempts to increase the limited mobility. The duration of symptoms was usually many months.

I have ordinarily treated subacromial bursitis with adhesions by manipulation (with general or local anesthesia) to separate the adhesions, followed by a program of exercises, such as wall climbing or swinging the arm in a stooping position or both. Large amounts of sedatives were usually necessary to control pain, and sometimes the pain persisted over long periods despite improvement in the range of motion. The first 2 patients in this group received the injections into the scalenus anticus muscle in an attempt to determine the cause of this severe and persistent pain. In 1 patient (A. Z.) there was immediate marked relief of pain, without recurrence by the time of discharge six weeks later. In the other patient (E. F.) there was no recurrence for five months. She was then given three additional injections, with satisfactory relief. The third patient (M. L.), who refused to exercise after manipulation, had intense pain and vasomotor phenomena associated with the bursal lesion. She exhibited a striking immediate response to injection, by relief of both pain and vascular spasm, partial relief being present even after one week. The fourth patient had severe pain and extremely dense adhesions; the injection gave distinct relief of pain. After twenty minutes block anesthesia of the brachial plexus was induced and she was manipulated. The clavicle was fractured in the course of manipulation. Although she complained of no recurrence of pain in the shoulder or arm at any time before discharge, it is likely that some slight pain was overshadowed by the pain of the fractured clavicle.

Two patients (A. K. and F. W.) were treated by manipulation with anesthesia, exercises and repeated injections into the scalenus anticus muscle, and I think that the injections resulted in considerably earlier relief of pain than would have been obtained otherwise.

Six patients exhibited a somewhat milder form of the condition, mainly in that the restriction of motion was not so extreme as in the severe forms. They were treated by exercises supplemented by repeated injections. Considerable improvement followed in each instance. One patient with bilateral extremely dense adhesions was treated by continuous traction in abduction for several days. The range of motion increased, but pain persisted. Exercises and additional injections into the scalenus anticus muscles resulted in considerable improvement.

One patient (D. R.) deserves particular comment. She came in complaining of dull pain in the shoulder and inability to elevate the arm, following a fall on the hand on the previous day. Injection had no effect on the pain, and roentgen examination disclosed a fracture of the head of the humerus, which was treated, with a good result. Three months later she complained of increasing pain and decreasing mobility in this shoulder. At this time injection relieved the pain and increased the mobility.

Every patient in this group experienced considerable relief of the constant pain immediately after injection, except for 2 who had little pain immediately prior to injection, and in these 2 the customary pain which appeared later was ameliorated for several days. Accompanying the relief of pain there was a definite increase in the mobility of the shoulder in most of the patients. The duration of relief was from several days to several months, in most instances varying with the progress of the bursitis. In those instances in which the adhesions had been separated by manipulation or exercises or both the relief often lasted for some time.

4. *Calcification in the Supraspinatus Tendon.*—Three patients presented themselves with severe pain in the shoulder due to calcification in the supraspinatus tendon. Two were in the acute phase of the condition and 1 in a subacute phase. The physical findings were typical—spasm of the shoulder muscles with severe pain on attempted motion and acute tenderness over the greater tuberosity. Only 1 patient exhibited tenderness over the scalenus anticus muscles.

Injection of procaine hydrochloride into the scalenus anticus muscle gave immediate relief of pain in all cases, accompanied with an increase in the range of motion. That the calcified area was not affected by the injection was evident from the residual limitation of motion in all cases and from the recorded persistence of the acute tenderness in 1 case. After the injection into the scalenus anticus muscle the patients were treated by injection of procaine hydrochloride into the calcified areas, with complete relief in the 2 cases of acute involvement and considerable improvement in the case in which the condition was subacute.

5. *Other Conditions Causing Pain in the Shoulder (Unresponsive to Injection).*—Two patients in this group suffered from narrowing of the intervertebral foramina and irritation of the roots of the brachial plexus, manifested in 1 case by intractable pain and in the other by paresthesias. Neither patient exhibited any response to injection. The third patient suffered from tendinitis of the long head of the biceps tendon in the bicipital groove. He also showed no response to injection into the scalenus anticus muscle but gave a striking response to injection of procaine hydrochloride into the peritendinous tissues. His original pain was well localized to the affected area.

TABLE 4.—*Calcification in the Supraspinatus Tendon*

Patient	Sex	Age	History	Physical Findings	Result of Scalenus Injection	Progress
1. H. C. W.	M	41	Pain in right shoulder, shooting down to fingers, progressively worse since onset 2 weeks before; severe while at rest, agonizing on motion	Rigid spasm of shoulder muscles; atrophy; acute tenderness at greater tuberosity; no scaleno tenderness	1/29/40: Immediate relief of throbbing pain; hand became warmer; voluntary abduction increased from 10 to 45 degrees	After 25 minutes the bursa and supraspinatus tendon treated with injection of 15 cc. of 1% procaine hydrochloride; abduction increased to 135 degrees, with only slight pain; by 1/31/40 there was no pain, even on abduction to 135 degrees; exercises prescribed
2. S. G.	M	44	Pain in left shoulder radiating to elbow, continuous and severe; onset 6 months before	Spasm of shoulder muscles, tender over anterior aspect of shoulder; scalenus pressure caused shoulder pain; abduction 40 degrees	2/13/40: Relief of pain for half a day	2/15/40: Calcified area, injection and aspiration; 2/19/40, pain and mobility much improved; 3/5/40, mild recurrence, calcified area, injection; 3/11/40, scalenus injection for recurrent pain
3. G. V.	M	65	3/5/40: Complained of pain in right shoulder Severe throbbing pain over upper deltoid for 2 days; onset 1 hour after a strain	Tender over greater tuberosity Spasm of shoulder muscles; acute tenderness of greater tuberosity and severe pain on motion; no scalene tenderness	No injection 4/25/40: Pain at rest disappeared entirely but still had pain on motion; abduction increased from 15 to 60 to 90 degrees; tenderness over greater tuberosity unchanged	Five roentgen treatments without improvement 4/26/40: Pain still much improved, abduction 30 degrees, calcified area injection; 4/29/40, very little pain, abduction 90 degrees, vastly improved

TABLE 5.—*Other Conditions Causing Pain in the Shoulder*

Diagnosis	Patient	Sex	Age	History	Findings	Result of Scalenus Injection	Progress
1. Narrowed Intervertebral foramina	S. M.	F	74	Severe pain in left shoulder for 6 months; progressively worse; pain from below ear down to finger tips	Slight limitation of internal and external rotation; roentgen study of cervical spine showed encroachment on intervertebral foramina between C4 and C5 and between C5 and C6	6/12/39: No relief; repeated in 10 minutes; no relief	Four doses of thiamine chloride, 50 mg. each, by vein without benefit; subacromial bursa treated by injection of procaine hydrochloride; pain became worse; 5 roentgen treatments to cervical spine with trifling improvement
2. Narrowed Intervertebral foramina	J. D.	M	63	Numbness and tingling in fingers of left hand for 2 years; pain in shoulder for a brief period at time of onset	Slight swelling of index finger and slight dulling of sensation in hand; cervical spine showed marked hypertrophic changes and encroachment on intervertebral foramina on the left from C2 to C6 and on the right from C3 to C5 on roentgen examination	2/8/40: Caused pain down arm; 2/13/40, no improvement	2/13/40: Patient thought there was slight improvement
3. Tendinitis of biceps	A. B.	M	21	Constant dull pain at right shoulder for 5 years; sharp pain on movement	Pain localized over deltoid distal to acromion; slight local tenderness; shoulder normal to roentgen examination	2/8/40: No spontaneous pain prior to injection, but had pain on motion; the latter not affected by the injection	2/13/40: Bicipital groove, 20 cc. of 1% procaine hydrochloride; relief for 3 days; repeated on 2/20/40; relief until 2/26/40, when he had only slight pain on motion

It may be noted here also that in patient D. R. (table 3) injection of the anesthetic into the scalenus anticus muscle produced no relief of the pain associated with a fracture of the humerus.

A brief mention of the 6 other patients in this series will complete the story of this experimental period. Five patients had very mild forms of subacromial bursitis interpreted as due to roughening of the bursa by villi bands or adhesions and had intermittent variable pain. They had practically no pain at the time of the test injection, and the later findings were inconclusive. One patient had ill defined dull pain of five years' duration, following a fall, with no limitation of motion and no roentgen abnormalities. The result of injection was inconclusive.

#### MECHANISM OF PAIN IN THE SHOULDER

Although scalenus spasm, hypertrophy or fibrosis may cause pain in the brachial distribution and vascular disturbances in the affected arm, my observations indicate that pain is present much more frequently than are vascular disturbances and that mild forms of the scalenus anticus syndrome may be overlooked if one depends on the usual criteria for diagnosis.

In the group of cases classified as examples of the scalenus anticus syndrome neither traumatic lesions nor other discoverable lesions about the shoulder girdle or neck were present. The patients were definitely characterized by droopy postures, which would suggest that the progressively lower position of the shoulder girdle caused progressively increased tension on the brachial plexus or increased angulation over the first rib, which finally caused pain. Reflex spasm of the scalenus anticus muscle may have followed the pain and in turn caused a definite progression of symptoms. It seems more likely, however, that some unaccustomed activity or position may have caused a myositis of the scalenus anticus muscle, which in turn precipitated symptoms in a subject made vulnerable by poor posture or by anatomic peculiarities.

Two patients (M. K. and A. K.), aged 66 years and 53 years respectively, had bilateral pain in the shoulder which came on while they were lying in bed recovering from an operation. The patient who was given an injection after eleven days of pain had permanent relief, while the other, who was not treated for six weeks, had adhesions in the subacromial bursa. The precipitating factor in both cases may have been prolonged stretching of the neck. Several patients associated the pain with prolonged use of the arm in writing, typing or doing housework, such as washing; again the possibility of primary myositis appears.

A stronger argument for primary myositis is my observation that permanent or prolonged relief follows injection of procaine hydrochloride. Myositic lesions elsewhere in the body often respond to this treatment.

In the group classified under "scalenus syndrome following trauma" I think that the lesion was an injury to the scalenus anticus muscle—traumatic myositis. The muscle goes into spasm just as does an injured dorsal muscle and causes symptoms by disturbing the brachial plexus. When the muscle spasm is abolished by injection of procaine hydrochloride the symptoms disappear, to return either in a much milder form or not at all. I have observed similar phenomena after treating muscular sprains of the back and fractures of the transverse processes of the lumbar vertebrae by injection.

The patients in the first two groups may be regarded as having a lesion primarily in the scalenus anticus muscle. Relief from this lesion resulted in relief of symptoms.

Those patients who suffered from subacromial bursitis with adhesions had a different situation. Bursitis with adhesions may follow an injury to the shoulder, such as fracture of the neck of the humerus or acute traumatic subacromial bursitis. These are associated with some hemorrhage and exudation about the subacromial bursa. If the arm is immobilized at the side for a sufficient length of time, the bursal surfaces agglutinate. When finally motion is attempted, traction on the adhesions causes pain and motion stays restricted. Spasm of the scalenus anticus muscle may be incited by the pain and may then cause the characteristic radiation down the arm.

It can be noted in table 3 that all but 1 of the patients were over 50 years of age. Meyer<sup>11</sup> has shown that attritional degenerative changes occur commonly in the supraspinatus tendon with advancing years. This results in roughening of the floor of the bursa. If atraumatic spasm of the scalenus anticus muscle or traumatic myositis is the initial lesion and causes pain and muscle spasm, the immobility may allow the roughened bursal surfaces to agglutinate and to become densely adherent. My observations suggest that this sequence of events occurs frequently. If one compares the patients in table 3 with those in table 2 one can observe that those in the group in table 3 were older and came in for treatment on the average four and one-half months after onset, while the group in table 2 came for treatment on the average seven days after onset. The latter group had already some limitation of motion, which in an elderly patient would finally result in bursal adhesions.

I have demonstrated by injection that a considerable element of spasm of the scalenus anticus muscle is present in these patients with bursal adhesions. If nothing was done to separate the adhesions they incited a recurrence of the spasm after a variable period, and the condition remained unchanged. When the adhesions were separated by

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11. Meyer A. W.: Chronic Functional Lesions of Shoulder, *Arch. Surg.* **35**: 646-674 (Oct.) 1937.

manipulation and exercises or by exercises alone, the persistent pain due to scalenus spasm or fibrosis was substantially relieved by injection.

The intense pain experienced in the acute phase of calcification of the supraspinatus tendon is due in part to spasm of the scalenus anticus muscle. Injection afforded striking but limited relief. These observations parallel those of Bishop,<sup>8</sup> who described relief of the scalenus anticus syndrome after surgical removal of the deposits. In my cases the spasm did not recur after dispersal of the deposits by injection of procaine hydrochloride into the calcified area.

The patients in groups 3 and 4 may be regarded as having secondary lesions in the scalenus anticus muscle. Injection of procaine hydrochloride into this muscle identifies the lesion and relieves a great deal of the pain, which recurs after a short interval. Spasm of the scalenus anticus muscle usually continues until the primary bursal lesion has been disposed of and may continue much longer, owing probably to fibrosis in the muscle. After the primary lesion has been overcome, injection tends to give prolonged relief of the residual symptoms.

#### EFFECT ON THE SYMPATHETIC NERVOUS SYSTEM

With but few exceptions the injections were followed by striking ocular evidence of paralysis of the cervical sympathetic nerves. Less frequently there was vasodilatation in the arm. One cannot, therefore, exclude the possibility that the pain in many cases was due in part to a sympathetic reflex mechanism similar to that thought to be present after injuries elsewhere in the body and that interruption of these reflexes was responsible for the relief of pain. In favor of this view is the frequent presence of muscle atrophy in these patients. Against it is the very rare occurrence of vasospastic phenomena of marked degree, which were searched for in all the patients, as well as the observed duration of the sympathetic effect, which was usually only forty-five to ninety minutes, a period far shorter than the period of relief of pain.

#### DIAGNOSTIC VALUE OF INJECTION

While persistent localized tenderness over the scalenus anticus muscle with radiation of pain into the arm is a valuable diagnostic sign, it was present in only a small number of my cases. Slight or moderate tenderness was present in many cases, and no tenderness whatever could be elicited in a considerable number. Temporary paralysis of the scalenus anticus muscle produced by injection of procaine hydrochloride is a far more reliable method of estimating the role of the muscle in producing pain.

I made repeated attempts to demonstrate reduction of the radial pulse by rotating the head toward the affected side, extending the neck

and forcibly depressing the shoulder, but I was not able to identify a change in the pulse in any case. In 4 cases repeated measurements of the blood pressure on both sides, with the scalenus anticus muscle alternately tense and relaxed, showed no significant changes. Measurements of the blood pressure after injection also showed no changes. In 1 case oscillometric readings were made under similar conditions, and no significant changes were observed.

It is therefore likely that the glossy skin, muscle atrophy and coldness of the hand occasionally observed originate from irritation of the sympathetic nervous system rather than from actual compression of the subclavian artery.

#### SUMMARY AND CONCLUSIONS

Injection of procaine hydrochloride into the scalenus anticus muscle was used to determine the origin of pain in the shoulder in 40 patients. I gave 78 injections without serious untoward effects.

Injection of procaine hydrochloride into the scalenus anticus muscle is often accompanied by temporary anesthesia of the cervical sympathetic fibers.

Injection of procaine hydrochloride into the scalenus anticus muscle is a valuable diagnostic measure in determining the origin of pain in the distribution of the brachial plexus.

Injection of procaine hydrochloride is a therapeutic measure of some value when there is spasm of the scalenus anticus muscle of postural origin, due to trauma or to subdeltoid bursitis of the acute or chronic type.

Repeated injections may help to avoid the need for scaleniotomy.

# PAPILLOMA OF THE CHOROID PLEXUS

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Papilloma of the choroid plexus is a rare tumor; no single author's published experience encompasses more than 12 instances. For this reason alone it seems justifiable to collect the isolated reports, since the frequency of diagnosis and surgical treatment of tumors of the brain is ever increasing and since there are few persons with a neurosurgical or neuropathologic experience extending over a period of five years who have not had contact with at least 1 papilloma. This paper represents a collection of the 80 odd published case reports of papilloma of the choroid plexus, together with some emphasis on incidence, sites of origin, inferences as to growth characteristics, pathologic picture—with emphasis on the known seeding characteristic—and summarized surgical experience.

## INCIDENCE

Cushing's series of 2,023 tumors of the brain contained 12 papillomas of the choroid plexus; Elsberg's series of 878 contained 2; Tooth's series of 258 contained 3, and Peers's series of 188 contained none. In the aggregate of these series, then, the incidence is not quite 0.4 per cent, a figure that compares favorably with Cushing's published incidence of 0.5 per cent in his own series of tumors of the brain.

Table 1 shows the incidence of the tumor in relation to age. It is seen to occur at any age, with a great predilection for the first decades of life, a fact which is not generally appreciated, since the older reports are of sporadic individual cases in which the patients were chiefly adults. More recently, with the increased vigilance concerning tumor of the brain greater and greater numbers of papillomas occurring in children have been reported; indeed, in 1 case (Drucker), the patient was a full term stillborn baby. With patients grouped by decades, it now seems that the greatest incidence falls in the first decade of life.

Table 2 shows the incidence of the tumor at its favorite sites of primary growth. It will be noted that in this series the lateral ventricles and the fourth ventricle, with equal incidence, were the most favored sites, followed by the third ventricle. Of the tumors listed as of the third ventricle, 2 had extensions into the fourth ventricle by way of the aqueduct of Sylvius; 2 had extensions into one lateral ventricle, and 2 had extensions into both lateral ventricles by way of the foramina of Monro, so that only 6 were confined to the third ventricle. Van Wagenen



has pointed out that of the lateral ventricles the left is the one of predilection, and this observation is borne out by the present material (table 2). It seems justifiable to accentuate the fact that about 1 of 5 of the tumors occurring in the posterior fossa arises from the tufts of the choroid plexus that extend into or through the foramens of Luschka.

TABLE 1.—*Incidence of Tumor in Relation to Age*

Newborn to 11 months	9
1 year to 9 years	18
10 years to 19 years	11
20 years to 29 years	16
30 years to 39 years	9
40 years to 49 years	11
50 years to 59 years	6
60 years to 69 years	2
70 years to 79 years	1

TABLE 2.—*Incidence of Tumor in Relation to Site of Origin*

Right Lateral Ventricle	Left Lateral Ventricle	Both Lateral Ventricles	Third Ventricle	Fourth Ventricle	Foramen of Luschka	Spinal Cord
14	20	1	13	29	7	1
Total	35		13	36		1

TABLE 3.—*Location of Primary Tumor in Relation to Age*

	Lateral Ventricles	Third Ventricle	Fourth Ventricle	Spinal Cord
Newborn to 11 months	8	1	..	
1 year to 9 years	14	1	3	
10 years to 19 years	2	3	6	
20 years to 29 years	4	2	10	
30 years to 39 years	1	2	6	
40 years to 49 years	5	1	5	
50 years to 59 years	1	2	1	1
60 years to 69 years	1	1		
70 years to 79 years			1	

This location has been mentioned previously as an occasional site (Bailey; Cushing), but such a designation is definitely an understatement for this material.

Table 3 is perhaps the most informative of this series. It shows that within the first decade of life the tumor is almost exclusively one of the lateral ventricles, while in the second, third, fourth and fifth decades it may occur anywhere but most commonly occurs in the fourth ventricle. The discrepancy in the total numbers of cases in this and in the following tables is of course due to incomplete data in the several individual reports included in the tables.

The data available were not often complete enough to make possible any valid statement relative to the relation existing between this tumor and the sex of the host.

#### PATHOLOGIC CONSIDERATIONS

In the gross, papilloma of the choroid plexus is granular in appearance; it is grayish red to pinkish gray, according to the abundance of its blood supply, and often, particularly in the lateral ventricles, it bears a thin encasing membrane. This membrane may be closely applied to the papillae of the tumor or separated from it by an abundance of fluid so that the whole tumor has the appearance of a cyst with a mural nodule. In fixed specimens the membrane is more obvious, as is the cauliflower-like papillary arrangement of the tumor. Microscopically, the membrane is very delicate, at most only two to three cells in thickness. It is highly acellular, composed of the same type of tissue as the stroma of the papillae of the tumor and frequently rather heavily infiltrated with wandering cells of various kinds (fig. 1).

Histologically the stroma of the tumor is composed of delicate strands of very acellular, reticular, fibrous connective tissue (never glia),

TABLE 4.—*Site of Primary Tumor and Incidence of Seeding*

Lateral Ventricles	Third Ventricle	Fourth Ventricle	Spinal Cord
4	4	5	1

through which passes at least one capillary. The stroma is made up of primary and secondary stalks, and the subdivisions of the vascular tree of the individual papillae parallel the divisions of the connective tissue stalks. The epithelial covering is usually a single layer of cuboidal or low columnar cells which bear no cilia. In the more hyperplastic areas of the tumor the epithelial cells may be heaped up, without definite stratification but obviously with more than one layer. The cytoplasm of the epithelium is eosinophilic, and the nucleolus is usually in a basilar or middle position and deeply basophilic. The cytoplasm bears no blepharoplastin (Mallory) but has numerous vacuoles and basophilic and pigment granules that have elicited the attention of various investigators (Ciaccio and Scaglione; Davis; Zalka). In the cross section the epithelium is arranged circularly about the connective tissue core and its blood vessels.

Deposition of calcium in this type of tumor has been infrequently reported. It occurs in areas of degeneration and necrosis. No particular pathologic significance is attached to this, since calcified glomuses are frequently seen in normal brains and since Zalka has described this phenomenon as observed in the plexuses of old persons and of persons dying of non-neurologic and chronic diseases.

The seeding of this tumor was emphasized by Van Wagenen. Table 4 shows the incidence of seeding and the location of the primary tumor. When it is remembered that 2 of the tumors of the third ventricle had extensions into a lateral ventricle, it will be seen that the percentage



Fig. 1.—*A*, characteristic appearance of the tumor, showing its acellular stroma and delicate membrane. *B*, high power photomicrograph of *A*, showing the delicate membrane with infiltration of wandering cells.

of seeding is highest with tumors of the lateral ventricles. This is interpreted as evidence of viciousness in tumors of this location, as is the fact that in one third of the cases of seeding the phenomenon occurs within the first decade of life. From these observations, it is perhaps justifiable to conclude that had not the tumor killed its host early

the incidence of seeding from the lateral ventricle would be much higher. The explanation for seeding is obscure, but a ready assumption is that trauma to a wildly growing tumor mass within a dilated ventricle—and there is almost universally associated internal hydrocephalus—disengages tumor cells, which are carried away by the cerebrospinal fluid. Seeding appears to take place by way of the cerebrospinal fluid, since all secondary implants save possibly that in the single case of Hall and Fentress have shown the nodule to be in the subarachnoid space (fig. 2). The entire number of cases in which seeding occurred represents one fifth

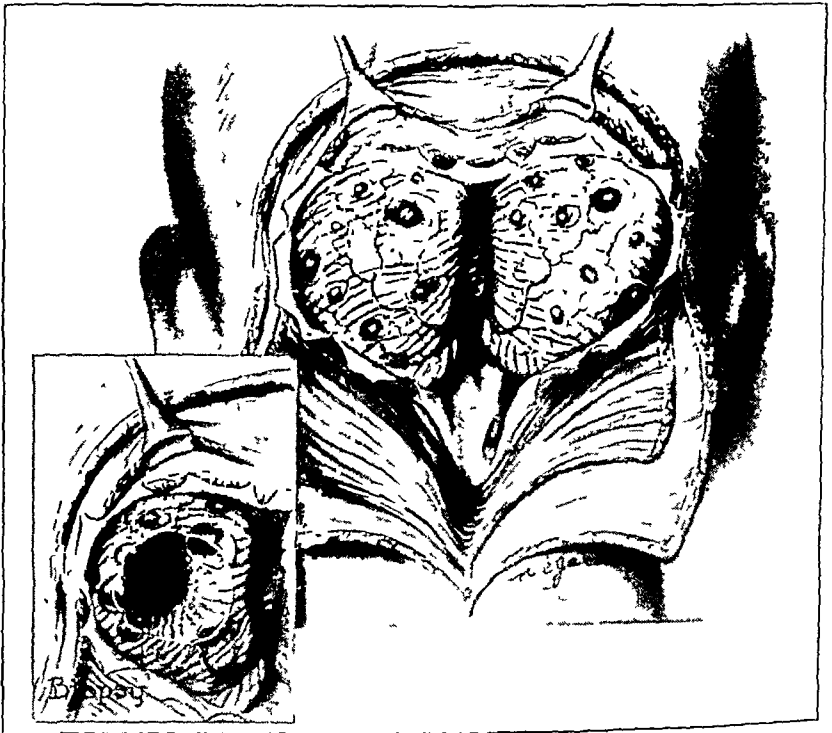


Fig. 2—Drawing of the tumor in Van Wagenen's case 3, showing secondary implants under the arachnoid over the cerebellar hemispheres

of the cases collected in this paper. It should be pointed out, however, that the recent greater number of surgical cases, as contrasted with the early autopsy cases, in a measure precludes the discovery of secondary nodules.

This tumor, particularly in the German literature, is frequently spoken of as a carcinoma. Academically and by strict definition this designation may be correct, since mitotic figures, reduplication of the epithelial layer, degeneration, necrosis and secondary distant growths are seen. But these signs of malignancy have not as yet been encountered in any single tumor reviewed in this series. Furthermore, all of the

intracellular changes save the appearance of mitotic figures have been observed in normal choroid plexuses in patients who died of a non-neurologic or chronic disease (Zalka; Ciaccio and Scaglione). In no instance has there been definite evidence of invasion of adjacent brain with obliteration of adjacent ependyma or pia; of neighboring glial reaction, such as occurs at the margins of an invasive primary or secondary neoplasm (Cox; Hassin), or of appearance of ciliated epithelium—the condition which normally obtains in embryonal and very young epithelium of the choroid plexus. Occasional mitotic figures are, more-



Fig. 3.—Photomicrograph of a secondary implant from the tumor shown in figure 2. Note that the tumor is not invading, but is pushing aside, the cerebellum.

over, often encountered in benign neoplasms. For these reasons it is doubted that papilloma of the choroid plexus is ever carcinomatous, with the ugly intimations that the term carries (fig. 3).

Internal hydrocephalus is an almost universal accompaniment of this kind of tumor. One notable exception to this rule was observed in the case reported by Hall and Fentress, in which the main body of the tumor was in the lumbar portion of the cord and smaller nodules occurred in the lateral ventricles. This condition, internal hydrocephalus, obtains whether or not there is mechanical obstruction to the circulation of

cerebrospinal fluid. This brings up the question whether by virtue of the increased secretory surface of the tumor there is an overproduction of cerebrospinal fluid. Illustrative cases in support of this contention are abundant in the literature, the most notable one being that reported by Davis, in which there was no obstruction but an enormous hydrocephalus in association with what was called hyperplasia of the choroid plexuses of both lateral ventricles. Further evidence can be gained from an occasional case in which an enveloping membrane is present. In such circumstances it is not infrequent to find the tumor existing as a mural nodule with its epithelium showing various degrees of degeneration, necrosis or ulceration and with its membrane greatly distended with a large volume of highly xanthochromic fluid. When the seedings and the adjacent structures are examined histologically, it is always seen that the tumor nodule proper is surrounded by a lake of fluid which presses aside the pia and the brain on one side and the arachnoid mem-

TABLE 5.—*Duration in Months of Symptoms in Various Age Groups*

	Months																							
	1 or Less	2	3	4	5	6	7	8	9	10	11	12	18	24	30	36	42	48	54	60	84			
Newborn to 11 mo..	4	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..			
1 to 9 years.....	4	..	..	1	1	..	..	2	..	1	..	..	..	..	..	..	..	..	..	..	..			
10 to 19 years.....	..	..	..	..	..	..	..	..	..	..	..	2	..	1	1	1	..	..	..	1	..			
20 to 29 years.....	2	1	1	3	..	1	1	..	..	..	..	..	1	..	..	..	..	1	..	..	..			
30 to 39 years.....	..	..	..	1	..	2	..	..	..	..	..	1	..	2	..	..	..	..	..	..	..			
40 to 49 years.....	..	1	..	..	..	..	1	..	..	1	1	..	..	..	..	..	..	..	1	1	..			
50 to 59 years.....	..	..	..	..	..	1	..	..	..	..	..	1	..	1	..	..	..	..	..	..	..			
60 to 69 years.....	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	1			
70 to 79 years.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1			

brane on the other. Again, an overabundance of cerebrospinal fluid was noted in the cases of Guillain and his associates and of Fehr. For a period of days Fehr's patient, who was thought to have serous post-traumatic meningitis, had from 200 to 300 cc. of cerebrospinal fluid withdrawn daily by lumbar puncture. So it seems more than probable that the tumor mass functions in the capacity of a normal choroid plexus and that the associated internal hydrocephalus in those cases in which it is not due to a mechanical obstruction is most probably due to an overproduction of cerebrospinal fluid.

#### LIFE HISTORY AND GROWTH CHARACTERISTICS OF THE TUMOR

Table 5 gives some notion of the life history of this tumor. If one were to plot the curve of relations expressed here, it would be a slightly curvilinear relation, with rapid progress of symptoms in the first decade of life and a gradual prolongation of the progress of symptoms as the higher decades were reached. This type of curve does not show a point to point relation between the site of the tumor and the progress of symp-

TABLE 6.—*Cerebrospinal Fluid in Cases of Papilloma of the Choroid Plexus*

Author	Pressure, Mm. H <sub>2</sub> O	White Blood Cells per Cu. Mm.	Protein, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Chlorides, Mg. per 100 Cc.	Comment
Grandclement and others	500-760 560	1 ..	44 ..	.. ..	.. ..	Positive Pandy reaction
Van Wagenen no. 1	Increased	0	225	43.5	720	Clear (right ventricle)
	Increased	Many crenated R.B.C.	2,062	54	708	Xanthochromic (left ventricle)
	Normal	0	240	57	768	Clear (lumbar sac)
no. 2	Increased	27	..	..	..	Globulin, 3+
Gromelski.....	250	712	..	..	..	Xanthochromic
Vincent and others, no. 2	..	4	18	..	..	
Dandy, no. 2.....	Increased	..	..	..	..	Xanthochromic ventricular fluid on tumor side; clear on opposite side
Faher.....	200	3	760	..	..	Clear and colorless
Kellner.....	170	3	..	..	..	Clear; globulin reaction negative
Hall and Fentress.....	250	7	..	..	..	Slightly xanthochromic; globulin, 3+
	350	2	..	..	..	
Graves and Fleiss.....	Normal	Many R.B.C., normal W.B.C.	..	..	..	Smoky and xanthochromic; no pellicle; no bacteria
Obarrio and others.....	350	..	..	..	..	Positive Wassermann reaction; positive globulin
Montanaro and Hanón	..	2	180	..	..	Negative Pandy, Nonne-Apptel and Weichbrodt reactions
Fehr.....	350	0	220	99	698	Cisternal fluid
Von Weber.....	..	3	40	..	..	Clear
Friedman and Solomon	..	..	..	..	..	"The spinal fluid was negative"
Bleyer and Siebert.....	Increased	Normal	..	..	..	Clear and colorless; no pellicle; no bacteria
Ebbs.....	..	..	Normal	Normal	683	Always blood tinged; never over 850 red blood cells per cu. mm.
Turner and Simon, no. 2	120 225	.. ..	.. ..	.. ..	.. ..	"Chemical examination was negative"
Saccone and Rosenthal	..	..	..	..	..	"Ayala Index of 5 revealed nothing"
Weinstein no. 1.....	Increased	60	..	..	..	Clear and colorless
no. 2.....	Increased	..	..	..	..	Clear and colorless
no. 3.....	310	..	..	..	..	Xanthochromic
Somerford.....	..	..	..	..	..	Lumbar puncture "three times without abnormal findings"
Caron and Samson.....	700	2	67	..	..	.....
Jefferson and Jackson	..	..	1,800	..	..	Ventricular fluid xanthochromic on affected side, normal on opposite side
Herren.....	400	3	56	..	..	Clear and colorless

W.B.C.= white blood cells; R.B.C. = red blood cells.

TABLE 7.—*Relation of Site of Primary Tumor to Surgical Morbidity*

Lateral Ventricles		Third Ventricle		Fourth Ventricle	
Recovered	Died	Recovered	Died	Recovered	Died
9	5	1	3	13	4

toms. The explanation must lie, then, in difference in local growth characteristics of this kind of tumor at various ages. In general, neurosurgeons have come to think of a tumor of the fourth ventricle as being quick to produce symptoms and of a tumor of a lateral ventricle as being slow, simply on the basis of adjacency of vulnerable structures and mechanical obstruction. The fact that the opposite is true of papilloma of the choroid plexus seems to point to the interpretation that when this tumor occurs in a child it is more malignant in its local growth characteristics than when it occurs in an adult.

#### CLINICAL DIAGNOSIS

The clinical diagnosis of this tumor is a problem indeed. Its rarity causes it not to suggest itself as a diagnostic possibility. Furthermore, a perusal of table 8 shows, in the number of wrong diagnoses by competent observers, that it must possess few of the diagnostic earmarks of the more common tumors of the brain. Experience tells that one is fortunate if one can lateralize the neoplasm without the aid of air studies. Examination of cerebrospinal fluid is of little aid in diagnosis. Table 6 shows the findings in 26 cases in which these data were given. However, it is felt that a tumor of this kind should suggest itself in the case of an infant with signs of obstructive or communicating hydrocephalus, particularly when there are lateralizing cerebral signs and xanthochromic fluid can be aspirated by puncture of the fontanel or other puncture. In passing, it is emphasized again that this type of tumor in the child is extremely vicious, in that its symptoms are obscure; it grows to enormous size; it is surgically difficult to handle because of its vascularity; and it causes death quickly. On the other hand, papilloma of the choroid plexus in the adult is more benign, though often having histologically apparent malignant characteristics.

#### SURGICAL EXPERIENCE

Surgical experience with this tumor began with Bielschowsky and Unger (cited by Van Wagenen) in 1902, and no one has published experience with more than 12 cases. Van Wagenen has reported a successful operation on an 8 month old infant after high voltage roentgen therapy. Dandy has had the unenviable experience of successfully removing a large nodule from a 3½ year old patient only to have it recur in six months at the site of excision. Data have been obtained on 30 operative cases, in which there were 10 deaths, a surgical morbidity of 33 per cent. No complete data can be obtained from this material for an estimation of surgical mortality, but it cannot be over 33 per cent. The greatest morbidity is in the middle decades of life, as is the greatest recovery percentage, since in only a few instances has the diagnosis been made and operation attempted with a patient under the age of 10 years.



Despite this, there does not seem to be a greater morbidity in adults from papilloma of the choroid plexus than from any other tumor similarly located (table 7).

Little can be concluded from these data regarding the use of roentgen therapy. Van Wagenen noted a decrease in the vascularity and size of the tumor in his patient, an infant, following roentgen therapy. However, because of the great vascularity of the tumor, which necessitated the use of the endotherm loop, he was not able to obtain a satisfactory biopsy specimen at his first stage operation, so that no case is on record in which a histologic study was made before and after irradiation. It is most probable, however, that irradiation is of benefit, since Jefferson and Jackson, using subtemporal decompression and roentgen therapy, were able to prolong for two years the life of a patient who had a right lateral intraventricular tumor. The usual postoperative course for a papilloma in a lateral ventricle is much shorter than this when the tumor has been incompletely removed and roentgen therapy has been withheld. Sai recently has reported alleviation of symptoms in the case of a patient who was given only high voltage roentgen therapy. In this case, however, the diagnosis of papilloma of the choroid plexus was only presumptive.

Recurrence has been reported in only 1 case, that of a 3½ year old boy. The tumor recurred in six months and attained a size greater than when first attacked. From so few data one can only mention in passing that papilloma of the choroid plexus does recur.

#### REPORT OF A CASE

Miss N. MacN., a 32 year old nurse with an extremely good social, educational and achievement background, presented herself with the complaints of "gingham or calico" colored scintillating scotomas, blurred vision and occasional transitory attacks of diplopia appearing when she was overtired.

The patient could not accurately date the onset of her illness but put it at something less than a year previously. At that time she had occasional transitory "gingham" scotomas, appearing first when she was overtired but increasing in frequency up to the time of examination, when the scotomas were almost continuously present. Also during this interval there had been transitory attacks of diplopia, never on more than three or four occasions and always when the patient was greatly fatigued. However, during this interval she had noted some difficulty in quickly focusing her eyes on new objects. Three months prior to examination she had begun to be troubled by blurred vision. She consulted a lay oculist, who told her that her glasses were too strong and prescribed new ones, which did not improve her vision.

The patient said that for many years she had had some unsteadiness when whirling, as in dancing. This unsteadiness, which consisted of staggering to the left, had not become exaggerated in the course of her present illness. For two years there had been a subjective sensation of increase in length of the right leg and an increase in size of the right hip. The glove and shoe sizes had not changed. There were no other complaints.

Site of Primary Tumor	Seeded
Right Intestine	5

Author	Cited by Van Wegenen	Age of Patient	Site of Primary Tumor	Seeded	Source of Material	Surgical Results	Comment
Gueard.....	Robin and Blondel.....	3 years	Right lateral ventricle	No	Autopsy	Death	No localizing symptoms
Leprat-Perrotin.....	Le Blanc.....	11 years	Fourth ventricle	No	Autopsy	Death	Localized as a cerebral tumor
Kelley.....		25 years	Left lateral ventricle	No	Autopsy	Death	
Chouppé.....		60 years	Fourth ventricle	Right cerebral cortex	Autopsy	Death	
Démange.....		11 years	Fourth ventricle	No	Autopsy	Death	
von Plath.....	Audry.....	42 years	Left lateral ventricle	No	Autopsy	Death	
Douty.....	Beneke.....	8 years	Both lateral ventricles	No	Autopsy	Death	
Beneke.....	Stroober.....	3 years	Left lateral ventricle	No	Autopsy	Death	
Stroober.....	Hess.....	45 years	Fourth ventricle	No	Autopsy	Death	
Hess.....	Lutigen.....	17 years	Third ventricle	No	Autopsy	Death	
Lutigen.....	Auvray.....	26 years	Left lateral ventricle	No	Autopsy	Death	
Auvray.....	Bruchanow.....	1½ years	Fourth ventricle	Fourth ventricle horn	Autopsy	Death	
Bruchanow.....	Heineberg.....	31 years	Third ventricle	Left temporal horn	Autopsy	Death	
Heineberg.....	Ribberts.....	? ?	Fourth ventricle	Fourth ventricle	Autopsy	Death	
Ribberts.....	Bielchowsky and Unger... Vikouroux.....	2½ years 50 years	Left lateral ventricle	No	Autopsy	Death	
Bielchowsky and Unger... Vikouroux.....	Rheindorf.....	? 43 years	Fourth and fourth ventricles	No	Autopsy	Death	
Rheindorf.....	Slaymaker and Elias.....	? 21 years	Right foramen of Luschka	No	Autopsy	Death	
Slaymaker and Elias.....	Boudet and Olmet.....	11 years	Fourth ventricle	No	Autopsy	Death	
Boudet and Olmet.....	Natonok.....	45 years	Fourth ventricle	No	Autopsy	Death	
Natonok.....	von Bouwldijk.....	15½ years	Right lateral ventricle	Both cerebral cortices	Autopsy	Death	
von Bouwldijk.....	Weygrandt.....	? 57 years	Fourth ventricle	No	Operation	Death	
Weygrandt.....	Goodhard.....	10 months	Fourth ventricle	No	Autopsy	Death	
Goodhard.....	Kornel.....	9 months	Left lateral ventricle	No	Autopsy	Death	
Kornel.....	Pethes.....	6 months	Right lateral ventricle	No	Autopsy	Death	
Pethes.....	Lorenzini.....	9 years	Left lateral ventricle	No	Autopsy	Death	
Lorenzini.....	Sachs.....	47 years	Third ventricle	No	Autopsy	Death	
Sachs.....	Friesel.....	10 years	Fourth ventricle	No	Autopsy	Death	
Friesel.....	Okabe.....	55 years	Fourth ventricle	No	Autopsy	Death	
Okabe.....		74 years	Both lateral ventricles and third ventricle	No	Autopsy	Death	
		5 months		No	Autopsy	Recovery	Correctly localized



TABLE 8.—Summary of Collected Cases of Papilloma of Choroid Plexus—Continued

Author	Age of Patient	Site of Primary Tumor	Seeded	Source of Material	Surgical Results	Comment
Fahr.....	29 years	Right lateral ventricle	No	Autopsy	.....	Diagnosed as unlocalized cerebral tumor
Kelner.....	34 years	Fourth ventricle	Cerebellum	Autopsy	.....	Diagnosed as cerebral tumor
Hall and Pentress.....	61 years	Third ventricle and left lateral ventricle	Cerebrum, cerebellum, spinal cord	Autopsy	.....	Diagnosed as metastatic tumor of cord
Graves and Gleiss.....	9 months	Left lateral ventricle	No	Autopsy	.....	Unlocalized during life
Fincher.....	26 years	Right lateral ventricle	No	Operation	Recovery	Localized by ventriculography
Obarrío and others.....	30 years	Fourth ventricle	No	Operation	Recovery	Localized correctly
Montanaro and Hanon.....	29 years	Left foramen of Luschka	No	Autopsy	.....	Localized correctly
Fehr.....	23 years	Fourth ventricle	No	Autopsy	.....	Diagnosed as serous meningitis
Von Weber.....	42 years	Left lateral ventricle	No	Operation	Death	Diagnosed as temporal lobe glioma
Tönnis						
Case 1.....	14 years	Fourth ventricle	No	Operation	Recovery	Localized correctly
Case 2.....	18 years	Right lateral ventricle	No	Operation	Recovery	Diagnosed as temporal lobe glioma
Friedman and Solomon.....	20 months	Left lateral ventricle	No	Autopsy	.....	Localized to left hemisphere
Bleyer and Siebert.....	6 months	Left lateral ventricle	Left lateral ventricle	Autopsy	.....	Diagnosed as tuberculous meningitis
Ebbs.....	14 months	Right lateral ventricle	No	Autopsy	.....	Diagnosed as idiopathic hydrocephalus
Turner and Simon						
Case 1.....	27 years	Third ventricle	No	Operation	Death	Unlocalized
Case 2.....	55 years	Third and fourth ventricles	No	Operation	Death	
Saccone and Rosenthal.....	48 years	Fourth ventricle	No	Autopsy	.....	Diagnosed as multiple sclerosis
Weinstein						
Case 1.....	10 weeks	Left lateral ventricle	No	Autopsy	.....	Diagnosed as meningitis because of pleocytosis
Case 2.....	14 months	Right lateral ventricle	No	Autopsy	.....	Diagnosed as tumor of right cerebral hemisphere
Case 3.....	45 years	Left lateral ventricle	No	Operation	Death	Localized by ventriculography
Cohen.....	43 years	Fourth ventricle	No	Operation	Recovery	Localized correctly
Somerford.....	7 years	Third ventricle and left lateral ventricle	No	Autopsy	.....	"No localization possible"
Tados.....	11 months	Right lateral ventricle	No	Autopsy	.....	Diagnosed as hydrocephalus
Quaron and Samson.....	41 years	Third ventricle	No	Autopsy	.....	Correct localization
Jefferson and Jackson.....	29 years	Right lateral ventricle	No	Operation	Recovery	Localized by ventriculography
Drucker.....	Newborn	Left lateral ventricle	No	Autopsy	.....	Tumor measured $4 \times 3 \times 3$ cm. at birth
Herren.....	32 years	Left foramen of Luschka	Vermis	Operation	Death	Localized by ventriculography

The patient's family stated that within recent months she had shown personality changes in the direction of forgetfulness, sloppiness in her work, apathy and general decrease in sociability.

The past history and family history were noncontributory.

The general physical examination showed her to be tall (5 feet 7 inches; 170 cm.), slender (112 pounds; 50.8 Kg.) and asthenic, without positive abnormalities. Measurements of the long bones of the two sides were identical, as were measurements of the two sides of the pelvis.

The neurologic examination revealed the following positive signs: The vision was normal; the fields were full, with a slight enlargement of the blindspots. There were no objective scotomas. There was bilateral choking of the disks (4 D.). There was nystagmus, both horizontal and rotary, on extreme left lateral gaze. There was no diplopia. Otherwise the cranial nerves were normal.

The motor and sensory systems were without positive abnormalities. There was a slight degree of dysidiadokokinesis of the left hand as the only symptom referable to the cerebellar system.

The deep tendon and superficial reflexes were present, normal and equal, and there were no pathologic reflexes and no clonus.

There were no signs, either primary or neighborhood, involving any of the cerebral centers.

The patient was seen by two neurologic consultants, both with wide experience, who reported essentially the same findings. The diagnoses of the three consultants were: hydrocephalus, cause unknown, and tumor of the brain, unclassified, of the left side of the cerebellum and of the right frontal area.

The patient was admitted to the hospital. Roentgenograms of the sinuses were normal; roentgenograms of the skull showed only a slight forward shift of the calcified pineal gland. The Kolmer reaction of the blood was negative. Routine studies showed the blood and the urine to be well within normal limits. A lumbar puncture was done with the patient in the reclining position and showed clear, colorless fluid under an initial pressure of 400 mm. of water; 3 lymphocytes per cubic millimeter of fluid, and a level of total protein of 56 mg. per hundred cubic centimeters. A Kolmer test of the spinal fluid gave a negative reaction.

Subsequent neurologic examinations showed only an equivocal Babinski sign on the right and bilateral unsustained patellar clonus.

On Dec. 19, 1939, a ventriculogram was made, air being injected only into the left lateral ventricle. Subsequent roentgenograms showed a moderate degree of symmetric dilatation of the lateral and third ventricles. No air could be visualized in the fourth ventricle, despite two attempts by routine manipulation. A cerebellar craniotomy was immediately performed. Before the very tight dura of the posterior fossa was opened, a right ventricular tap was attempted. A subcortical vessel was ruptured and bled briskly. The needle was left in place until the bleeding stopped. Then the left lateral ventricle was tapped, and clear fluid was recovered. The dura of the posterior fossa was then opened widely, and after the arachnoid of the cisterna magna was opened a grayish brown granular tumor was seen under the left lobus biventer, presenting over the left tonsil and extending through the foramen magnum onto the spinal canal to the second cervical vertebra. The lower pole of the tumor was dissected free, but the tumor was fragmented in its removal. The origin of the upper pole was not positively identified, but the operator felt that he was dealing with a psammomatous meningioma arising from the basilar portion of the occipital bone and that by luck rather than by skill he had dissected off the attachments to the basilar artery. The three large fragments that were preserved measured 2 by 2 by 1 cm. each

and weighed 6.5 Gm. These fragments the operator felt represented three fourths of the tumor. The dura over the cerebellum and the upper part of the cord was left open and the wound closed in layers in the usual fashion.

The immediate postoperative course was characterized by great restlessness without threatening changes in the vital signs. The patient was disoriented and irrational and showed hypesthesia on the left side and increase in the reflexes, with ankle and patellar clonus and a Babinski sign on the left. Daily lumbar punctures showed an increase in pressure, with the fluid at first rather bloody but clearing of free blood in two days. Choking of the disks did not subside. It was felt that probably bleeding from the subcortical vessel ruptured at the time of ventricular tap had allowed the collection of a subdural hematoma on the right side. Two days later, exploratory burr holes in the right temporal and frontal region failed to reveal subdural blood of clinical significance. The surgical specimen was at this time available for microscopic examination, and the tissue was readily seen to be a papilloma of the choroid plexus. Because the patient's condition had not improved, it was felt that most probably there was a tumor mass filling the fourth ventricle and that at the first operation only its extension through the foramen of Luschka had been removed. Six days after the original operation the cerebellar wound was reopened and a large accumulation of xanthochromic fluid was encountered. The right lateral ventricle could not be entered, but the left was readily tapped. The fourth ventricle was explored through the left lateral recess and by splitting the vermis; no tumor tissue was encountered. The patient's condition after this was unchanged. Several days later an attempt was made to tap the right ventricle again, and 40 cc. of chocolate-colored blood was aspirated. This was followed by clear cerebrospinal fluid. It was felt that an intraventricular clot had formed at the time of the first operation and that this procedure had drained it and ruptured its wall into the cerebrospinal fluid circulation. The patient complained bitterly of headache, vomited a great deal and was almost continuously nauseated for the next four days. Lumbar punctures, which up to this time had yielded clear fluid, now yielded deeply xanthochromic fluid, which cleared subsequently. The patient, after her early headache and vomiting, was clear mentally, sat up in bed and ate well.

The signs referable to the upper motor neurons disappeared, but low grade choking persisted. Subsequently and slowly she became drowsy and irresponsive. A ventricular tap yielded clear fluid with flecks of fibrin. Some methylene blue was introduced into the right lateral ventricle and was not recovered from either the left ventricle or the lumbar sac. With the patient in the cerebellar position, needles were introduced into the posterior bodies of both lateral ventricles and a third into the anterior body of the right through the previously placed burr holes. The right ventricle was emptied and gently irrigated. Some perfusion fluid with phenolsulfonphthalein was introduced under low pressure into the left ventricle and recovered from the anterior needle in the right ventricle. The process was repeated, perfusion through the anterior needle in the right ventricle until all air had been emptied from the two ventricles and the perfusion fluid recovered from both posterior needles. Subsequent lumbar puncture failed to recover the dye. After this the patient's course was slowly downhill, and she died on March 8, 1940, after a long interval of unconsciousness.

Postmortem examination of the brain revealed dense, impermeable adhesions that bound the cerebellum to the floor of the left lateral recess and also the vermis to the obex. There was, then, an obstructive internal hydrocephalus. Further sections revealed on the right side a large intracerebral hemorrhagic cavity the wall of which was lined by shaggy, necrotic brain and encapsulated firm blood clot.

A point of communication between this hemorrhagic cavity and the right lateral ventricle was identified, and the wall of that ventricle was stained with blood pigment and covered with a thin layer of organized fibrin. On the inferior surface of the vermis was a second plaque of tumor.

## SUMMARY

Eighty odd cases of papilloma of the choroid plexus are reviewed and the pathologic considerations mentioned. It is pointed out that the recent literature emphasizes the occurrence of this tumor in childhood as a tumor almost exclusively of the lateral ventricles, while in adulthood it is most likely to occur in the fourth ventricle. The growth characteristics of the tumor in each age group are mentioned; the occurrence of seeding is reemphasized; the difficulty in clinical diagnosis is noted, and the surgical experience with this tumor is reviewed. A case report is included.

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# PRIMARY TORSION AND INFARCTION OF THE APPENDICES EPIPLOICAE

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Among the many acute intra-abdominal conditions which produce clinical problems, primary lesions of the appendices epiploicae are relatively rare. Because of this, the clinician or surgeon often does not consider lesions of these structures in the differential diagnosis of intra-abdominal disease. Consequently the clinical diagnosis of primary torsion, infarction or inflammation of the appendices epiploicae has, according to the literature on this subject, never been made. One must admit, however, that recognition of disease of these structures is very important from the standpoint of offering the patient an accurate prognosis. There are many variations from the typical picture, and often the clinical and laboratory findings are not sufficiently significant to be of any help in diagnosis. Our object in conducting this review was to discover, if possible, any facts that could add to our diagnostic acumen when confronted with the aforementioned conditions.

In 1936, Fiske<sup>1</sup> was able to collect only 42 cases of primary disease of the appendices epiploicae from the entire medical literature; he added 2 of his own cases. Since then, other instances of this condition have been reported by Davis,<sup>2</sup> Walker,<sup>3</sup> Piulachs,<sup>4</sup> Poirier,<sup>5</sup> Micheli,<sup>6</sup> Baumeister, Hargens and Morsman<sup>7</sup> Campbell<sup>8</sup> and Eliason and Johnson.<sup>9</sup> In all, these cases comprise a total of 55 reported to date.

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In the period between 1915 and 1939, 7 cases of primary acute lesions of the appendices epiploicae were observed at the Jewish Hospital. In no case was a correct diagnosis of the condition made preoperatively; the lesion was discovered at operation only after thorough exploration of the peritoneal cavity failed to reveal any other cause for the acute abdominal episode. There is no train of symptoms or signs characteristic of this disease. Occasionally abdominal pain is the only presenting symptom; this may be definitely localized or vague and ill defined. Usually symptoms referable to the vermiform appendix are so predominant that attention is likely to be diverted from the underlying abnormality. The clinical importance of recognizing the true etiologic factor is obvious. It is our purpose, therefore, to describe this syndrome and to discuss the pathologic mechanism of its production.

#### ANATOMIC CONSIDERATIONS

The epiploic appendages are small pouches of peritoneum laden with fat. Each appendage encloses small branches of the arteries and veins which vascularize the corresponding segment of the colon. The appendages are situated along the cecum, the colon, the upper part of the rectum and occasionally also the vermiform appendix. They are chiefly found along the transverse and pelvic segments of the colon, where they are larger than elsewhere; at the base of the appendix they are usually rudimentary. The appendices epiploicae also bear a definite relation to the taeniae coli and are often arranged in two rows, one situated medial to the anterior taenia and the other lateral to the posterolateral taenia. They rarely appear in three rows and less often in one row. The altered position of the suspended transverse colon changes the relative position of the taeniae and consequently also of the appendices epiploicae; the anterior taeniae become posteroinferior, and the posterolateral taeniae become anterior.

The epiploic appendages vary considerably in size, shape and contour in various parts of the colon; as a rule they are longest in the sigmoid flexure. However, the size appears to vary also with the general state of body nutrition; they are largest and most conspicuous in obese persons and in those who have recently lost weight. The latter fact indicates that the fat in the appendages is utilized more slowly than is the remaining body fat. The average length of the epiploic appendage is 3 cm.; these structures have been reported, however, to have reached a length of 15 cm. (Linkenfeld<sup>10</sup>). They vary in shape, being tubular, saccular, cylindric, multilobulated, conical or leaf shaped. The free borders may be flat, rounded, serrated, fringed or indented. Their attachment to the intestinal wall may be by a wide or a narrow base. In children the

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10. Linkenfeld, F.: *Deutsche Ztschr. f. Chir.* 92:383, 1908.

appendices epiploicae are more or less inconspicuous, but they have been shown to appear as early as the fifth month of fetal life.

The physiology of the appendices epiploicae is still not clearly defined and is the subject of much controversy. A review of the literature reveals several conceptions which appear to be based more on supposition than on actual fact. Thus Robinson<sup>11</sup> in his monograph concluded that the appendices epiploicae are associated with the movement and absorption of fluids in the large bowel. Other investigators have expressed the belief that they serve as protective agents, like the omentum, and act as barriers against injury. In support of the latter idea is the fact that they are often found adherent to areas which are the seats of inflammatory reactions. However, this agglutinative property is characteristic of all peritoneal surfaces. Patterson<sup>12</sup> suggested that they may act as protective external colonic pads, thus enabling the colon to ward off the adjacent organs in its peristaltic excursions. Cheever, in a discussion of Patterson's paper, stated the opinion that the appendices epiploicae are entirely functionless.

In spite of the voluminous literature on this subject, we were impressed with the need for a painstaking study of the anatomic and physiologic aspects of the appendices epiploicae. For this reason a detailed study of these structures was conducted by one of us (B. P.). The blood vessels to the colon were injected with a mixture of red lead and starch in order to trace the smaller branches to their terminations in channels of the intestinal wall.

It was noted that the vessels to the large bowel do not enter the wall directly at the mesenteric border as do the vasa recti of the small intestine. Instead, they divide at the mesenteric border of the colon within the peritoneal fat; then they encircle the wall of the bowel subperitoneally, giving off small branches to the wall. In so doing they carry along a layer of protective subserous fat which is directly continuous with the fat in the mesentery. The main vessels continue into the fat of the appendices epiploicae, where they generally describe an inverted U-shaped arch from which branches run into the intestinal wall proximally and into the epiploic fat distally. The main vessel finally enters the intestinal wall adjacent to the border of the tenia (fig. 1). It appears, therefore, that the appendices epiploicae are merely protective fat pockets for the redundant intestinal vessels when the intestinal wall is collapsed. This safety mechanism of vascular redundancy is obviously necessary to prevent compression of the vessels and obliteration of their lumens when the bowel is distended. In all probability also the appendices epiploicae

11. Robinson, R.: *Anatomie et pathologie des séroappendices*, Thesis, Paris, no. 282, 1908.

12. Patterson, D. C.: *New England J. Med.* **209**:1255, 1933.

have some protective and absorptive function, since they consist of vascular tissue covered by peritoneum similar to the greater omentum. In contrast to the omentum, however, their surface area is small, and their vascularity is not as great; this reduces their functional capacity to a minimum.

There follow reports of 7 cases of acute lesions of the appendices epiploicae which have been observed at the Jewish Hospital. The lesions are of interest from the standpoint of difficulty of recognition, and the data indicate that such lesions occur often enough to warrant considera-

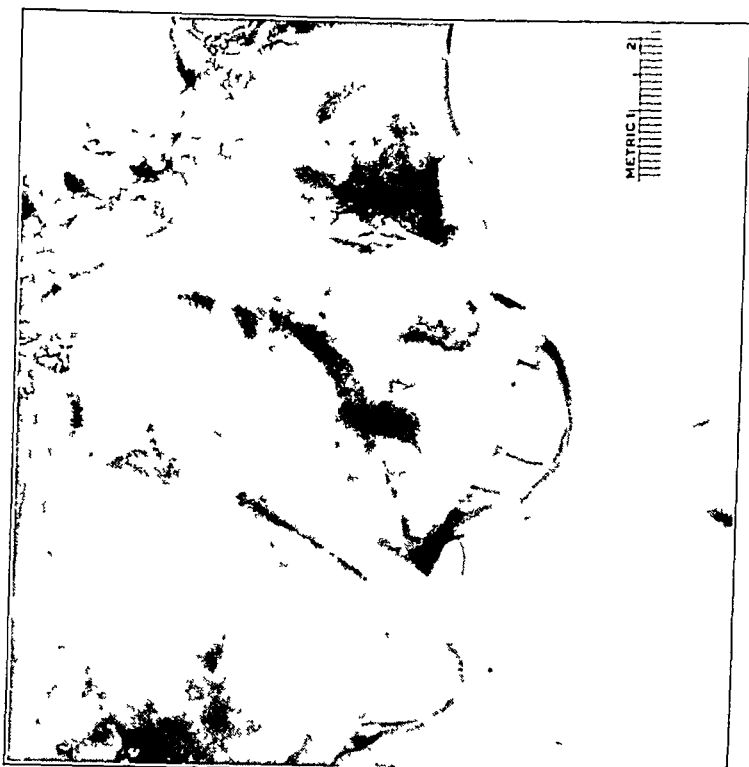


Fig. 1.—Blood supply to the appendices epiploicae, showing the main blood vessel leaving the colon and entering the epiploic appendage, where it describes a U-shaped arch. After giving off branches to the appendix, the vessel reenters the colon.

tion in all cases of acute intra-abdominal lesions, especially in adult obese patients.

#### REPORT OF CASES

CASE 1.—E. D., a 42 year old white woman, was admitted to the hospital because of pain in the left lower quadrant of the abdomen of five days' duration. The pain was at times sharp and sticking and at others dull and achy; it had been especially severe during the past twenty-four hours. Two hours before hospitalization the patient felt "something give" within the abdomen, and the pain appeared to subside somewhat. She also complained of frequency of urination and had to urinate every half hour.

On physical examination the patient was seen to be obese. She was apparently not acutely ill. The temperature was 101 F., the pulse rate 100, the respiratory rate 20 and the blood pressure 130 systolic and 90 diastolic. There were exquisite tenderness and moderate spasticity in the left lower quadrant. Vaginal examination showed tenderness in the left fornix. The urine was normal. The blood count revealed 10,000 white blood cells per cubic millimeter, with 73 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes and 3 per cent monocytes.

The clinical impression was that of perforated sigmoiditis, for which she was operated on through a left gridiron incision. As the peritoneal cavity was opened, an irregular, firm mass was seen about the sigmoid flexure. The free surface of this mass was mottled yellow, gray, blue and red in different areas. It proved to be a twisted gangrenous epiploic appendage. The mass was excised after ligation of its base, and the patient made an uneventful recovery.

Pathologic examination of the specimen disclosed diffuse hemorrhagic extravasations and suppuration within a mass of fatty tissue.

CASE 2.—A. D., a 20 year old woman, was admitted to the hospital with the complaint of pain in the right lower quadrant of the abdomen, of two days' duration. The pain had been intermittently sharp and cramplike and had become progressively more severe. During the past twenty-four hours she had been suffering also from frequency of urination and dysuria.

The past history was essentially irrelevant except for occasional head colds and transient mild attacks of pain in the right lower quadrant of the abdomen since the age of 10 years. The menstrual history was normal; the last period had occurred three weeks before.

On examination the patient appeared well developed and well nourished but acutely ill. The temperature was 99 F., the pulse rate 80, the respiratory rate 20 and the blood pressure 132 systolic and 88 diastolic. There was marked tenderness in both lower quadrants of the abdomen, especially on the right side, where rebound tenderness was also elicited. Rectal examination revealed no abnormality; the urine was normal, and a normal blood count was recorded.

The clinical impression was that of acute appendicitis. At operation, through a right gridiron incision and with spinal anesthesia, the peritoneum was opened, and a large quantity of serosanguineous fluid was found in the peritoneal cavity. Attached to the ascending colon was a blue-black mass which measured 4 by 3 by 0.5 cm.; this proved to be a gangrenous epiploic appendage, the gangrene being caused by torsion. The mass could be easily separated from the bowel, and it was excised after ligation of its base. The vermiform appendix was also removed, and the patient made an uneventful recovery.

Pathologic examination of the epiploic appendage showed a hemorrhagic infarct caused by thrombotic occlusion of its venous system. The vermiform appendix appeared normal.

CASE 3.—L. H., a 28 year old woman, was hospitalized because of severe abdominal pains of eight days' duration. At its onset the pain was referred to the left lower quadrant, but on the fifth day of illness it radiated to the right lower quadrant. On the fourth day of the illness the pain was accompanied with chills and fever.

The menstrual period was normal; the last period had ended one week before the patient entered the hospital. She had been married for six years and had three children, who were living and well.

She was well developed and well nourished. She was very tender in the left lower abdominal quadrant and presented a small palpable mass in the left anterior lumbar region. The urine was normal. The blood count showed 16,100 white

blood cells per cubic millimeter, with 65 per cent polymorphonuclear leukocytes and 35 per cent lymphocytes. Roentgen examination of the kidneys revealed no abnormality. The clinical impression was that of sigmoiditis or diverticulitis of the colon.

With the patient under general anesthesia a midline incision was made in the lower part of the abdomen and the peritoneal cavity was entered. An irregular blue-black mass was found attached by means of a broad pedicle to the sigmoid flexure; all other abdominal viscera appeared normal. The mass as well as the vermiform appendix was removed, and the patient made an uneventful recovery.

Pathologic examination of the specimen revealed thrombotic occlusion of the epiploic veins with hemorrhagic infarction of the epiploic appendage. The vermiform appendix appeared normal.

CASE 4.—A. E., a 45 year old woman, was admitted to the hospital with pain in the lower part of the abdomen, of two day's duration. She had felt a mass in the middle of the lower part of the abdomen for one year, and she had suffered from dysuria for the past two months.

Her present illness dated from two years previously, when an umbilical hernioplasty was performed. After the operation the patient suffered from transient attacks of dysuria. One year before the onset of her present illness she felt a small, painless, hard mass in the middle of the lower part of the abdomen. Two days before entering the hospital she suddenly experienced severe pain and tenderness in the region of the mass. This had become progressively more severe, and there had been a moderate rise in temperature.

During the past two years the patient had become obese, and she had also noted a change in her menstrual cycle; menstruation had become irregular, and the flow was scant.

Examination revealed her to be obese and acutely ill. The temperature was 101 F., the pulse rate 90 and the respiratory rate 24. There was pronounced emphysema of the chest, and the heart was enlarged to the right and to the left of the sternum. The abdomen was pendulous and showed a transverse scar about 4 inches (10 cm.) in length in the region of the umbilicus. Below the scar there was a firm, round, nodular mass measuring about 2 inches (5 cm.) in diameter. It appeared to be connected with the abdominal wall and was very tender. The urine gave a 3 plus reaction for albumin; many epithelial and white blood cells and occasional granular casts were seen. The blood count showed 12,000 white blood cells per cubic millimeter, of which 80 per cent were polymorphonuclear leukocytes and 20 per cent were lymphocytes.

The preoperative impression was that of abscess of the abdominal wall. With the patient under general anesthesia a median incision was made below the umbilicus. An edematous, red-blue mass was found adherent to the anterior parietal peritoneum. Further investigation disclosed this mass to consist of five appendices epiploicae of the sigmoid, matted together and twisted about their pedicles. No other pathologic lesion was noted in the abdomen. The gangrenous appendages were excised, and the patient made an uneventful recovery.

Pathologic examination of the specimen disclosed hemorrhagic extravasations and round cell infiltration into the various fat lobules.

CASE 5.—S. H., a 20 year old man, was seized with a sudden attack of sharp pain in the epigastrium three days before entering the hospital. Twenty hours after the onset of his illness the pain became localized in the right lower quadrant of the abdomen, where it remained. It was associated with persistent nausea. The past history revealed a similar transient attack of pain seven months before.

Examination revealed the patient to be well developed and well nourished. He was apparently acutely ill. The temperature was 100 F., the pulse rate 120 and the respiratory rate 24. There were marked tenderness and slight muscle spasm in the right lower quadrant of the abdomen. The urine was normal. The blood count showed 10,200 white blood cells per cubic millimeter, of which 73 per cent were polymorphonuclear leukocytes and 27 per cent were lymphocytes.

A diagnosis of acute appendicitis was made. A right McBurney muscle-splitting incision was made with the patient under general anesthesia. Exploration of the peritoneal cavity disclosed a small yellow and red mass arising from the lateral cecal wall and adherent at one point to the mesoappendix. This mass was taken to be a gangrenous epiploic appendage, and it was excised. The vermiform appendix was also removed, and the patient made an uneventful recovery.

Pathologic examination of the specimens revealed an atrophic vermiform appendix and an infarcted epiploic appendage infiltrated with red and white blood cells.

CASE 6.—B. B., a 48 year old man, was admitted to the hospital with the complaint of pain in the right lower quadrant of the abdomen, of three days' duration. The pain was sudden in onset; it was sharp and intermittent, and it persisted until the patient entered the hospital. There were also a mild degree of nausea and a slight rise in temperature. The past history revealed that the patient had had a large reducible right inguinal hernia for the last twenty-five years, for the relief of which he wore a truss. This occasioned no unusual symptoms.

Examination showed him to be well developed and well nourished. He was apparently not acutely ill. The temperature was 99 F., the pulse rate 84 and the respiratory rate 24. The only salient findings were tenderness and slight muscle spasm in the right lower quadrant of the abdomen. There was also found an easily reducible right inguinal hernia. Rectal examination revealed no abnormality.

A diagnosis of subacute appendicitis was made. With the patient under general anesthesia, a McBurney muscle-splitting incision was made and the peritoneum was entered. The vermiform appendix appeared normal. Further exploration revealed a twisted red-blue gangrenous epiploic appendage of the transverse colon, which was loosely adherent to the anterior parietal peritoneum just below the level of the umbilicus. Appendectomy and excision of the epiploic appendage were performed, and the patient made an uneventful recovery.

Pathologic examination revealed a normal vermiform appendix and infarction of the epiploic appendage caused by venous thrombosis of its vessels.

CASE 7.—W. K., a 44 year old man, was admitted to the hospital with the complaint of abdominal pain, nausea, vomiting and fever of six days' duration. The onset of the attack was sudden, and the pain was cramplike, intermittent and localized to the epigastrium. Three days later the pain became increasingly more severe and shifted to the right lower quadrant of the abdomen. The temperature was slightly elevated but rose to 103 F. on the day of his entering the hospital. The patient had had two loose stools during the past twenty-four hours.

During the past three years he had been known to have pulmonary tuberculosis, and nine months previously he had been discharged from a sanatorium with arrested bilateral apical tuberculosis.

Physical examination revealed him to be well developed and well nourished. He was acutely ill. The temperature was 102 F., the pulse rate 112, the respiratory rate 28 and the blood pressure 114 systolic and 80 diastolic. There were dulness to percussion in the apex of the left lung and diminished breath sounds and moist rales in that of the right. There was tenderness over the entire lower part of the abdomen, especially on the right. There were also marked spasticity and

rebound tenderness in the right lower quadrant of the abdomen. Rectal examination showed tenderness on the right side. The urine was normal. The blood count showed 13,000 white blood cells per cubic millimeter, with 78 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes.

A diagnosis of acute appendicitis was made, although the possibility of ileocecal tuberculosis was also considered. With spinal anesthesia, a McBurney muscle-splitting incision was made. The peritoneum was thick and edematous, and free serosanguineous fluid was found in the peritoneal cavity. A thick, red, indurated mass about 8 cm. long, with a bulbous tip, was brought out from the region of the appendix. The mass was excised with the phenol knife after ligation of its base; the patient made an uneventful recovery. Subsequent examination of the sputum, the fluid from the peritoneal cavity, the stools and the urine revealed no evidence of tubercle bacilli. The Wassermann reaction of the blood was negative.

A study of the excised tissue showed on section closely packed yellow and red lobules of adipose tissue. Microscopic examination of the specimen disclosed lobules of fat separated by loose fibrous connective tissue septums and enclosing numerous dilated and engorged thin-walled blood vessels. There were also diffuse hemorrhagic extravasations within the fat lobules.

#### COMMENT

In summarizing the findings in our entire group we have tabulated the incidence of the disease according to age, sex, pain, etc. An analysis of the diagnostic facts regarding this disease shows that of the 7 patients whose cases are reported in this paper 4 were women and 3 were men. Their ages ranged from 20 to 48, with an average of 35.5. The salient features of these 7 cases are summarized in the accompanying table. The onset of symptoms was acute in all 7 cases. The average duration of symptoms before operation varied from two to eight days. The character of the pain varied; it was described as sharp by 4 patients, cramp-like by 2 and dull by 1. In 2 patients the pain was localized immediately in the left lower quadrant; in 2 others, in the right lower quadrant, and in 1 it persisted in the middle of the lower part of the abdomen. In the remaining 2 patients the pain began in the epigastrium and later shifted to the right lower quadrant. Low grade fever occurred in 4 cases, nausea in 3, vomiting in 1, constipation in 1, loose stools in 1, dysuria in 2, and frequency of urination in 2.

Three patients presented past histories which may have had bearing on their present illness. Thus, in 1 instance the patient experienced transient attacks of pain in the right lower abdominal quadrant for ten years prior to the present attack of pain in the same quadrant; in 1 other there were transient attacks of abdominal pain similar to that noted before operation for seven months before the onset of the present illness. In the last case the patient had been operated on for an umbilical hernia two years previously. She noted a mass below the umbilical scar one year after the hernioplasty; this mass proved to be a large infarcted epiploic appendage.



Physical examination revealed that 5 patients were well nourished and 2 were obese. Only 3 patients appeared acutely ill on entering the hospital. The average temperature varied from 99 to 102 F.; in 4 instances it was 100 F. or over. Tenderness over the affected area was observed in all cases. In 2 patients it was located in the right lower quadrant; in 2, in the left lower quadrant; in 2 over the entire lower part of the abdomen, especially on the right side, and in 1, in the middle of the lower part of the abdomen. Three patients showed mild to moderate muscle spasm over the tender area, and 2 showed rebound tenderness.

*Data on Seven Cases*

Case.....	1	2	3	4	5	6	7
Age.....	42	20	28	45	20	48	44
Sex.....	Female	Female	Female	Female	Male	Male	Male
Duration of symptoms.....	5 days	2 days	8 days	2 days	3 days	3 days	6 days
Pain at start.....	Left lower quadrant	Right lower quadrant	Left lower quadrant; right lower quadrant	Lower mid-abdomen	Epigastrium; right lower quadrant	Right lower quadrant	Epigastrium; right lower quadrant
Tenderness.....	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rigidity.....	Yes	No	No	No	Yes	Yes	Yes
Nausea.....	No	No	No	No	Yes	Yes	Yes
Vomiting.....	No	No	No	No	No	No	Yes
Constipation.....	No	No	No	Yes	No	No	No
Nutrition.....	Obese	Good	Good	Obese	Good	Good	Good
Abdominal mass.	No	No	Yes	Yes	No	No	No
Temperature, F....	101	99	100	100	100	99	102
White blood cells, per cu. mm.....	10,000	8,000	16,000	12,000	10,000	9,000	13,000
Preoperative diagnosis	Perforated sigmoiditis	Acute appendicitis	Diverticulitis	Abscess of abdominal wall	Subacute appendicitis	Subacute appendicitis	Acute appendicitis
Postoperative diagnosis	Torsion of epiploic appendage	Torsion of epiploic appendage	Infarct of epiploic appendage	Torsion of epiploic appendage	Infarct of epiploic appendage	Torsion of epiploic appendage	Infarct of epiploic appendage

In 1 patient there was found a palpable mass in the left anterior lumbar region, and in another a mass was felt just below the umbilicus. Rectal and vaginal examination elicited tenderness over the affected side in 2 instances.

The white blood cell count was normal for 2 patients; for the others it was elevated, ranging between 10,000 and 16,000 per cubic millimeter. The differential count showed a range of 65 per cent to 80 per cent polymorphonuclear leukocytes.

The preoperative diagnosis was acute or subacute appendicitis for 4 patients, sigmoiditis or diverticulitis for 2 patients and abscess of the abdominal wall for 1 patient. At operation there was a striking simi-

larity in the pathologic picture in all 7 patients; the lesion consisted of an irregular mass mottled yellow, red and blue-black. The mass was firm and indurated, and in 4 patients it was found adherent to the surrounding tissues. The largest of these masses was suspended from the cecum and measured 8 by 2 cm.

The distribution of the lesions was as follows: 2 were associated with the cecum and showed no evidence of torsion; 1 was suspended from the ascending colon and was found twisted on its pedicle; another, similar mass with a twisted pedicle was associated with the transverse colon. In 3 patients the lesion was in the appendices epiploicae arising from the sigmoid flexure; 2 of these were found twisted at operation. In 2 instances serosanguineous fluid was present in the peritoneal cavity. In 5 patients the vermiform appendix was also removed, although in none of these did this structure show gross evidence of pathologic change. In 1 instance an infarcted epiploic appendage arising from the cecum was mistaken at operation for a gangrenous vermiform appendix, for which reason it was removed. Subsequent pathologic examination of the specimen, however, proved it to be a gangrenous epiploic appendage and not an inflamed vermiform appendix. All the 7 patients operated on made an uneventful recovery.

Pathologic examination of the specimens again showed the same picture for all 7 patients. It consisted of irregular, dense yellow, red and blue lobules of adipose tissue separated by thin fibrous connective tissue septums. In 2 instances there was found gross evidence of venous thrombosis of the infarcted appendices epiploicae. In 1 of these patients the appendage, arising from the sigmoid flexure, was found not twisted at the time of operation; another appendage, arising from the transverse colon, showed torsion. The outstanding features in all 7 cases were marked congestion, edema and hemorrhage into the fat and into the connective tissue septum (fig. 2). There was, in addition, a mild inflammatory reaction, in which the exudate consisted for the most part of monocyctic cells, polymorphonuclear leukocytes and occasional plasma cells and histiocytes. In 2 patients there was a marked large mononuclear cell infiltration, and in another, with a twisted epiploic appendage, there was an abundant polymorphonuclear cell infiltration suggestive of suppuration.

In general it may be said that there is no train of symptoms or signs characteristic of the disease. Abdominal pain is more or less a constant feature and is described as sharp or colic-like. The location of the pain in the abdomen varies according to the seat of the lesion in the colon. In 4 of the patients the pain was referred to the right lower quadrant, in 2 to the left lower quadrant and in 1 to the middle of the lower part of the abdomen. Another striking symptom in the syndrome of this disease is the disproportion between abdominal tenderness, the duration of symptoms and abdominal rigidity. The abdomen is usually locally

and definitely tender to deep palpation, and the abdominal rigidity is not nearly as marked as one might expect it to be when the possible duration of the complaint and the definite tenderness are considered. Another outstanding symptom of the disease is the marked hyperesthesia of the skin. We have found the same to hold true in cases of infarction involving the larger omentum (Pines and Rabinovitch<sup>13</sup>). The normal leukocytic reaction is only moderately disturbed, and the temperature in the uncomplicated case is not elevated.

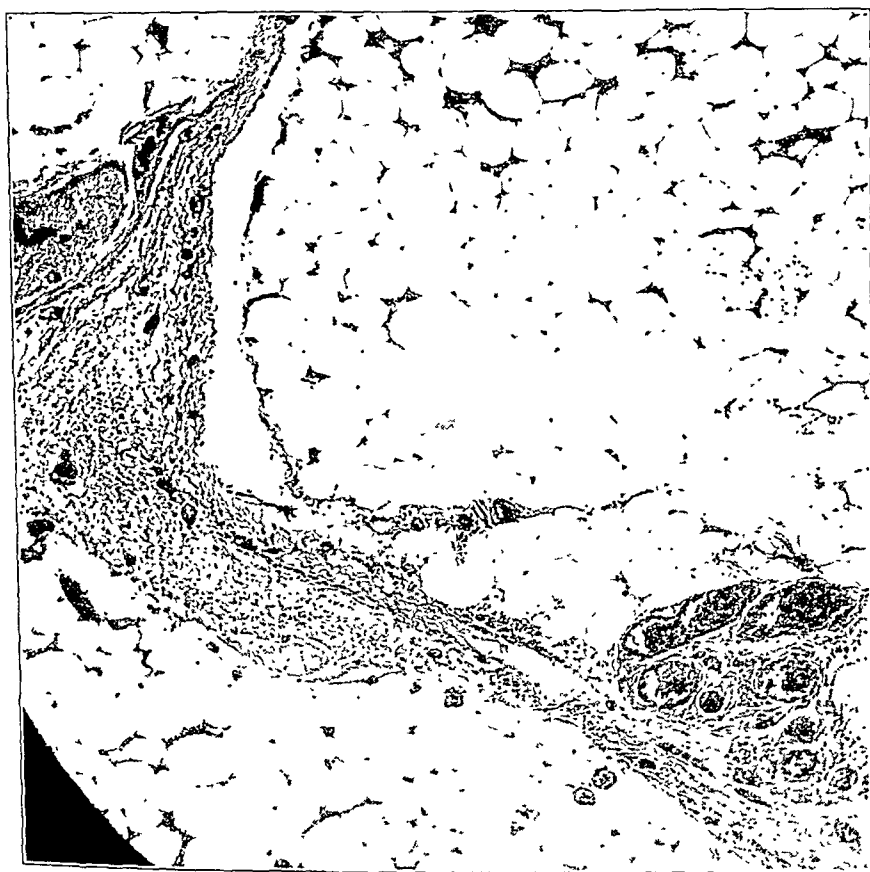


Fig. 2.—Infarct of the epiploic appendage, showing thrombotic occlusion of the blood vessels, hemorrhagic extravasations between the various fat cells and round cell infiltration into the connective tissue septums.  $\times 100$ .

The diagnosis of torsion and infarction of the appendices epiploicae is usually very difficult, primarily because of the rarity of the condition and the frequency with which other forms of peritoneal irritation are seen. It is especially difficult to make a differential diagnosis from acute appendicitis, diverticulitis, sigmoiditis, mesenteric thrombosis and strangulated internal hernia. Almost all of these lesions present indications

13. Pines, B., and Rabinovitch, J.: *Surg., Gynec. & Obst.* **71**:80, 1940.

for laparotomy; when the abdomen is open and exploration reveals the true nature of the disease, proper treatment may be instituted.

The cause of torsion of the appendices epiploicae is still obscure and subject to a great deal of controversial discussion. The prevalence of the disease among well nourished and obese persons is significant and at once suggests a causal relation. It is well known that in the obese the appendages tend to be abnormally long, a condition which permits ready twisting because of mechanical reasons (Morestin<sup>14</sup>). Davis expressed the opinion that the long and narrow pedicle of the epiploic appendage is primarily responsible for the production of torsion. We have noted, however, that torsion may occur with equal frequency in the short and wide pedicle. In none of our patients was there a history of sudden exertion or trauma which might have initiated torsion. Such factors as strong abdominal muscle contractions or intestinal peristalsis have been considered by some as precipitating factors, but no definite proof has been offered by the advocates of this hypothesis. It has been suggested by Payr<sup>15</sup> that, since the appendical veins are longer than the corresponding arteries, the former might become twisted around the latter, with the production of infarction because of venous occlusion. Such a condition is particularly prone to occur in cases in which a digestive plethora of the intestinal vascular system exists and in which the distal end of the epiploic appendage is heavier and contains more fat than the proximal portion. It has been shown that a physiologic splanchnic plethora exists during the process of digestion; this is characterized by engorgement of the mesenteric veins. The venous engorgement is most pronounced in the more distal and dependent portion of the appendages. It is easily conceivable that a sudden exertion or trauma during this phase of digestive plethora may stretch and traumatize the delicate venous wall and result in local thrombosis and subsequent infarction. In further support of such an idea is the fact disclosed by one of us (J. R.<sup>16</sup>) in a series of experiments, namely, that a forceful pull on the jugular vein in the rabbit, injuring its endothelial lining, results in the formation of a clot at the site of injury.

In the event of sudden or gradual twisting of the appendices epiploicae or in cases of primary thrombosis of the epiploic vessels aseptic gangrene usually sets in provided no secondary infection supervenes. The gangrenous tissue is subsequently organized, with the formation of a fibrous tissue mass; this mass may become dissociated from the remaining normal tissue and be cast off into the peritoneal cavity as a foreign body. In 1 of the patients cited such a fibrous mass was found almost completely detached from the base of the epiploic appendage.

14. Morestin, H.: *Bull. et mém. Soc. anat. de Paris* **87**:391, 1912.

15. Payr: *Arch. f. klin. Chir.* **62**:501, 1902.

16. Rabinovitch, J.: Unpublished data.

Deville, in 1851, found a number of free bodies in the peritoneal cavity, and in 1 instance he noted that an epiploic appendage was about to fall off spontaneously. However, it was not until 1863 that Virchow called attention to the relation of these corpora aliena adiposa, as these bodies have been termed, to the appendices epiploicae. He stated that the increased fat in the appendages of the obese patients is chemically split and calcified and that the increased weight causes obstruction to the circulation, resulting in necrosis and spontaneous sloughing. No mention was made of primary torsion and infarction of the appendices epiploicae as the basic mechanism in the formation of these loose bodies; the latter have been shown to reach a large size (that of a hen's egg) and to contain calcium and occasionally also fibrocartilage. Klingenstein<sup>17</sup> collected from the literature 12 cases of loose intra-abdominal bodies which presumably originated from the appendices epiploicae.

Inflammation of the appendices epiploicae may be superimposed on an area of infarction. It may also result from direct extension of an adjoining inflamed viscus, especially the colon, as in the case of diverticulitis. Primary inflammation of the epiploic appendages is a rare occurrence; several cases have been reported in the literature. A careful scrutiny of the surgical material at the Jewish Hospital failed to reveal any similar cases. We have observed, however, inflammatory reactions in epiploic appendages which have been primarily the seat of infarction.

The various lesions described may be quite innocuous so far as the future health or life of the patient is concerned. They have been shown, however, to produce morbid changes, and in a number of instances they led to death. Thus, Patterson, Klingenstein, Poirier and Baumeister, Hargens and Morsman have reported cases of intestinal obstruction produced by lesions of the appendices epiploicae. In 1 case inflamed appendices epiploicae on either side of the colon became adherent to one another and constricted the bowel at three different levels. The patient died after a cecostomy. Poirier was able to show roentgen evidence of constriction of the terminal portion of the ileum caused by an inflamed epiploic appendage of the sigmoid flexure.

Torsion and inflammation of the appendices epiploicae may go on to ultimate formation of a localized abscess, or generalized diffuse peritonitis may set in, resulting in death, as described by Seelye and in 2 other cases reported in the literature.

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17. Klingenstein, P.: Surg., Gynec. & Obst. 38:376, 1924.

## RAPID TISSUE DIAGNOSIS

COMPARISON OF MICROSCOPIC DIAGNOSES OBTAINED FROM  
TERRY'S RAZOR SECTIONS AND FROM PARAFFIN  
SECTIONS IN 4,326 BIOPSIES

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WICHITA, KAN.

Rapid tissue diagnosis during operation has lately fallen into discredit. While many surgeons still are enthusiastic about it, leading pathologists have recently criticized this method as not only unreliable but unnecessary.

According to Simpson,<sup>1</sup> "the Frozen Section Fetish appeals to the surgeon mainly because it adds to the drama in the operating theatre. What better impression can the surgeon make upon visiting practitioners than to toss a specimen to a waiting pathologist and await his return a few minutes later, often out of breath, to give a diagnosis. If the surgeon has faith in his preoperative diagnosis and his gross observations at the time of the operation, such a practice is unnecessary."

Every one will agree with Simpson that rapid tissue diagnosis as an act of surgical showmanship is unworthy of the pathologist as well as of the surgeon. A simple remedy against the abuse of this method is provided by a request by the pathologist for an appointment made the day before the operation and by a reasonable consultation fee.

Simpson opened his encyclical against rapid tissue diagnosis with the citation of an actual observation in which, like a trained seal, the pathologist caught a small bit of breast tissue tossed by the surgeon, rushed to the laboratory, made a hurried microscopic examination, ran back to the operating room and gasped "scirrhus carcinoma." This true story misses the point. If the gross appearance of the "well developed carcinoma was so characteristic that it should have been recognized as such by the surgeon," there was certainly no need for the pathologist to run to his microscope. He should have diagnosed the tumor by gross inspection right in the operating room. After all, the surgeon who consults the pathologist wants an expert diagnosis but cannot dictate the method of diagnosis.

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From the Department of Pathology of the St. Francis Hospital and the Sedgwick County Tumor Clinic.

1. Simpson, W. M.: The Frozen Section Fetish, editorial, *Am. J. Clin. Path.* 7:96, 1937.

I am not particularly interested in the question whether rapid tissue diagnosis is necessary. I leave the indications to the surgeon and trust that he will request tissue diagnosis during operation in the interest of the patient and not to glorify himself. As a pathologist, I am much more interested in Simpson's second point, that rapid tissue diagnosis is hazardous and unreliable.

Simpson stated that in a few of the larger clinics certain pathologists have acquired great skill in the preparation and diagnosis of fresh frozen sections, while in smaller laboratories an accurate diagnosis is often impossible. He concluded that any diagnostic method which yields good results only in the hands of a few experts is not adaptable to the average hospital laboratory.

I do not know on what facts Simpson bases his verdict. Certainly there are no statistical data in the literature which allow a comparison between rapid and paraffin sections. Not by generalities, but only by accurate reports on the results of rapid tissue sections can it be determined whether this diagnostic method is justified or, as Simpson concluded, should be abandoned.

The present paper is based on a comparison of microscopic diagnoses obtained from rapid tissue sections and those obtained from permanent paraffin sections in 4,326 biopsies.

#### TECHNIC

For ten years I have been using Terry's razor sections as the most favored routine method of diagnosing tumor tissue during operation. I follow Terry's<sup>2</sup> original procedure, fastening the specimen with two pins to a cork plate and cutting it with straight biconcave razor. I have given Terry's modification,<sup>3</sup> in which a safety razor blade in a self-made microtome is used, a fair trial, but have returned to his original method.

Its principle is that one need not cut tissue very thin to get histologic detail; relatively thick sections are made with the razor and stained superficially, on one side only, with neutral polychrome methylene blue. The slice of moist tissue, with the stained surface uppermost, is covered with a cover glass and examined with transmitted light from a 100 watt frosted mazda bulb. Since only the upper cell layer is stained and the light is transmitted through the thick, unstained part of the tissue, one has the impression of seeing a perfectly thin microtome section. The nuclei are stained deep blue, while connective tissue and muscle fibers are light rose. Few artefacts are encountered, since freezing, fixing, boiling and dehydrating are completely avoided.

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2. Terry, B. T.: A New and Rapid Method of Examining Tissue Microscopically for Malignancy, *J. Lab. & Clin. Med.* **13**:550, 1928.

3. Terry, B. T.: An Inexpensive Easily Made Safety Razor Blade Microtome with Technic Especially Useful in the Immediate Microscopic Diagnosis of Tissue, *Am. J. Clin. Path. (Tech. Supp.)* **7**:69, 1937.

The microscopic picture remains for about six minutes; then the stain fades slowly. Sections may be restained, or, if more material is available, a new section may be cut.

I prefer Terry's supravital technic for the following three reasons:

1. The greatest disadvantage of frozen sections is that the available tissue may be completely used up by the rapid method, and the subsequent employment of other methods is impossible. The preliminary cutting of razor sections does not exclude the later use of paraffin embedding. Even thin razor sections are usually thick enough to be cut in paraffin. Moreover, the staining of sections with polychrome methylene blue does not prevent the subsequent staining of these with

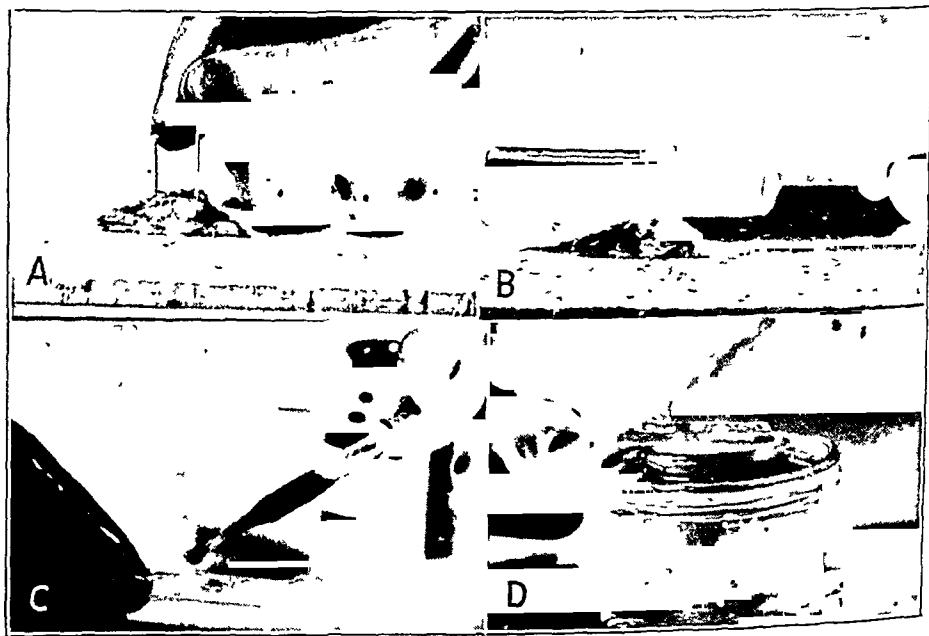


Fig. 1.—Terry's technic. *A*, the biopsy specimen is fastened to a cork board with two pins. *B*, with a biconcave razor a thin slice is cut off. *C*, the section is stained superficially for a few seconds with polychrome methylene blue. *D*, the stain is washed off with water. After covering with a cover glass, the section is examined microscopically by transmitted light.

other stains, for the methylene blue is extracted completely when the tissue is dehydrated.

2. The second reason I prefer Terry's method is that it is so simple that the pathologist is entirely independent of a technician in the preparation of the sections. Examination of the fresh surgical specimen by sight and by touch, selection of the block, the cutting sensation with the razor, the avidity of the tissue for the stain—all these furnish essential and often conclusive information to the pathologist which a ready-made



microscopic frozen section handed him by the technician may never reveal.

3. In rapidity, Terry's method is unsurpassed by any other histologic procedure. In less than one minute the tissue is cut and stained. Therefore Simpson's objection that it is not possible during operation to make several rapid sections from different areas of the biopsy specimen certainly does not hold for Terry's method. Without causing delay for the surgeon, it is easy not only to diagnose the local lesion but to determine accurately the margin that should be given from a benign or malignant tumor and to ascertain whether lymph nodes near the local

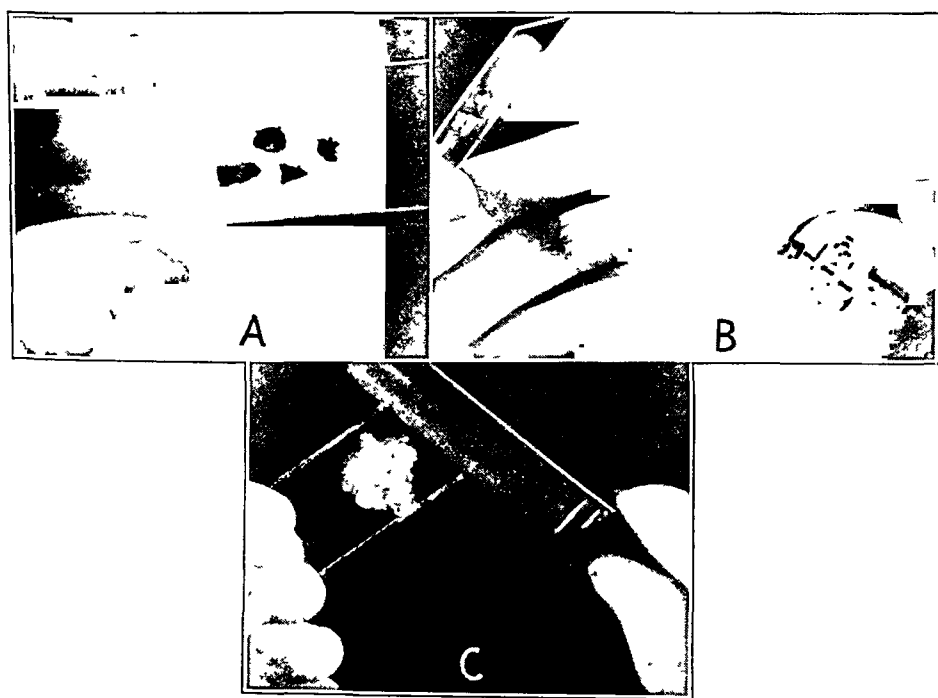


Fig. 2.—Hall's modification of Terry's section. This is used for specimens too small or too friable to fasten on the cork board. *A*, the tissue fragments are placed on a glass slide. *B*, the lower surface of the glass slide is frozen with the ethyl chloride spray. *C*, the upper portion is cut off so that a thin, flat slice remains on the slide. From this point the procedure is continued as shown in figure 1 *C*.

lesion show metastases. Histologic control of the whole operation for tumor is made practicable by this method.

While Terry's original method can be applied successfully to the great majority of biopsy specimens, there is one definite limitation, namely, an extremely small specimen. If it is possible to fasten the piece of tissue with two pins on a cork plate, i. e., if the diameter is at least 5 mm., a good razor section can be obtained as a rule. Curettings or

small fragments of soft tumors of the bladder or rectal polyps are not suitable for this method. For these, Hall's <sup>4</sup> modification has proved of greatest value; it is superior to the use of the freezing microtome. The curettings are placed on a glass slide, and the lower surface of the slide is sprayed with ethyl chloride until the tissue is frozen. With a razor held parallel to the glass slide the upper portion of the tissue is cut away so that a flat piece of tissue about 2 mm. thick remains on the slide. The tissue is allowed to thaw out and is stained exactly like an ordinary Terry section.

TABLE 1.—*Comparison of Microscopic Diagnoses Obtained from Terry's Sections and Paraffin Sections in 4,326 Biopsies*

Year	Cases	Benign	Malignant	Complete Agreement, Percentage	Partial Agreement, Percentage	Doubtful, Percentage	Disagreement, Percentage
1935.....	613	438	175	95.8	2.5	0.6	1.1
1936.....	669	503	166	95.2	2.6	0.9	1.3
1937.....	912	673	239	95.8	1.1	0.6	2.5
1938.....	1,049	760	289	94.6	1.8	0.5	3.1
1939.....	1,083	773	310	95.7	0.8	1.4	2.1
Total....	4,326	3,147	1,179	95.4	1.5	0.8	2.3

TABLE 2.—*Comparison of Microscopic Diagnoses Obtained from Terry's Sections and Paraffin Sections from Different Organs*

Tissue	Cases	Complete Agreement, Percentage	Disagreement, Percentage
Skin.....	815	90.7	4.3
Cervix.....	786	97.6	2.0
Corpus uteri.....	697	93.6	0.7
Lymph node.....	141	90.1	4.3
Mouth.....	284	93.6	2.5

## RESULTS

The results in this series of 4,326 biopsies are recorded in table 1. Complete agreement between the histologic diagnoses obtained from razor sections and those obtained from paraffin sections was found in 95.4 per cent of all cases. Malignancy or benignancy was correctly recognized in 96.9 per cent by the rapid method. In 0.8 per cent of all cases the Terry method did not permit a clearcut diagnosis and the surgeon was advised to proceed with his operation on clinical judgment or to await a final diagnosis made from paraffin sections. In 2.3 per cent there was disagreement between the diagnoses obtained from Terry's section and those obtained from paraffin sections.

In table 2 a comparison of histologic diagnosis is made according to different organs. It is evident that noncarcinomatous lesions of

4. Hall, W. E. B.: A Modification of Terry's Method of Rapid Sectioning for Soft Tissues, *Arch. Path.* 25:854 (June) 1938.

lymph nodes are the hardest tissues to diagnose by the supravital method. Hodgkin's disease, lymphosarcoma and simple chronic lymphadenitis may look much alike in the razor sections. On the other hand, metastatic carcinoma in lymph nodes is as easily recognized as the primary tumor. The relatively large number of failures in cutaneous biopsies is explained almost entirely by the extremely small size of most of the specimens of skin. Often taken from the face, too sparingly, to avoid disfiguring scars, they are usually too small to be held with two pins on the cork plate. When the size is sufficient, neoplastic tissue is easily recognized in Terry's sections. Inflammatory and metabolic cutaneous lesions may present great diagnostic difficulties to the pathologist also in paraffin sections and often require special staining methods.

The results in diagnosing endometrial scrapings were much better after Hall's modification of Terry's method was adopted.

#### COMMENT

My results in the diagnosis of supravital sections are in accord with the view held by Wood,<sup>5</sup> that in the vast majority of cases a correct histologic diagnosis can be made in the operating room in a few minutes after removal of the specimen but that it is impossible to make correct diagnoses in 100 per cent of the cases. No general acceptance or condemnation can be made in regard to the usefulness of rapid tissue diagnosis. The success depends on familiarity with a given procedure and on the experience of the microscopist. Other essential factors are: the location of the laboratory near the operating room; the willingness of the pathologist to use the rapid tissue method on every occasion, whether the surgeon requests it or not; the courage of the pathologist to admit his failure when the specimen cannot be diagnosed by supravital technic, and the understanding of the surgeon that rapid tissue diagnosis will fail in 3 per cent of all cases.

From a ten year experience I am convinced that surgeons who thoroughly understand the limitations of the method appreciate the possibility of having a correct microscopic diagnosis in all but a few cases during operation. Even if the surgeon is not interested in rapid tissue diagnosis, I cannot see how the pathologist in his daily routine can get along without it. For years I have made Terry's razor sections from every tumor specimen which comes to my laboratory, whether the surgeon requests it or not. The gross diagnosis of tumor tissue is stressed more and more (Ewing<sup>6</sup>). There is no better way to gain experience in the gross diagnosis of tumors than by razor sections.

5. Wood, F. C.: The Diagnosis of Cancer, J. A. M. A. **95**:1141 (Oct. 18) 1930.

6. Ewing, J.: Causation, Diagnosis and Treatment of Cancer, Baltimore, Williams & Wilkins Company, 1931, p. 43.

Using this method, the pathologist can associate in his mind the gross and the microscopic picture within a few minutes, while the preparation of paraffin sections brings a delay of several days. The selection of suitable blocks for paraffin embedding is also much facilitated by first obtaining Terry sections from different portions of a specimen.

The microscopic examination of fresh tissue, which played a large part in the earlier days of histopathology, seems at present a lost art. Henke,<sup>7</sup> in his "Guide to Tumor Diagnosis," pointed out that the microscopic diagnosis of fresh tissue is neglected without reason by those who rely on the modern embedding and staining methods and that in some cases only the examination of fresh tissue enables one to recognize the finer cell structures as they exist in the living stage. To do justice to the patient, no examination of tumor tissue can be regarded as complete unless all three diagnostic methods are employed—the inspection and palpation of the gross specimen, the microscopic examination of supravital preparations and, finally, the leisurely study of paraffin sections.

No experienced pathologist will deny that rapid tissue diagnosis has its limitations, but the art of its employment lies in a thorough understanding of these limitations. There are, on the other hand, such great advantages in the use of rapid tissue diagnosis that it should be used in all biopsies in addition to paraffin sections.

Terry's supravital technic is as simple, as fast and as economical as a bacteriologic smear and is, in my opinion, an indispensable tool of the modern laboratory, large or small.

#### CONCLUSIONS

In the vast majority of cases of tumor a correct histologic diagnosis can be made during operation within a few minutes after removal of the specimen. In 4,326 biopsies, the microscopic diagnoses obtained from rapid tissue sections and paraffin sections were in complete agreement in 95.4 per cent of all cases.

Terry's supravital technic is superior to the frozen section method. It should be adopted by surgical laboratories as the standard method of rapid tissue diagnosis.

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7. Henke, F.: *Mikroskopische Geschwulstdiagnostik*, Jena, Gustav Fischer. 1906, p. 12.

# SPINAL ANESTHESIA AND SURGICAL SHOCK

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AND

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BROOKLYN

A marked fall in blood pressure during an operation with general or local anesthesia is usually accepted as an indication of severe hemorrhage, surgical shock or both. This has led many surgeons to believe that the fall in blood pressure which regularly accompanies the induction of spinal anesthesia has equally grave significance. On the basis of the same kind of reasoning, various technics have been introduced either to prevent the fall in blood pressure or to raise the pressure after it has reached what is considered a dangerously low level, and it has been argued that spinal anesthesia is contraindicated in the presence of the hypotension secondary to traumatic shock, hemorrhage and peritonitis.

On the other hand, in a previous report one of us (Koster<sup>1</sup>) concluded, on the basis of 3,500 experiences with spinal anesthesia, that the fall in blood pressure, no matter how marked, is not of great significance and also that hypotension per se is no contraindication to the use of this anesthesia. Since then, over 10,000 additional experiences have confirmed this view and have led us to believe that there is a marked difference between the circulatory status of patients under spinal anesthesia and that of patients in surgical shock.

Recent studies<sup>2</sup> have shown that in cases of "surgical shock" not accompanied with hemorrhage the fall in blood pressure is preceded by marked hemoconcentration. In fact, it has been maintained that hemoconcentration, as evidenced by a rise in the red cell count, the hemoglobin concentration or the specific gravity of the whole blood, is a better index of the presence and severity of "shock" than is a fall in blood pressure.

To determine whether the fall in blood pressure which occurs during spinal anesthesia is similar to that associated with surgical shock, we studied the blood pressure and the concentration of hemoglobin in the blood before, during and after spinal anesthesia.

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From the Richard Morton Koster Research Laboratory.

1. Koster, H.: *Am. J. Surg.* 5:554, 1928.

2. (a) Blalock, A.: *Internat. Clin.* 1:144, 1933. (b) Scudder, J.: *Shock: Blood Studies as a Guide to Therapy*, Philadelphia, J. B. Lippincott Company, 1940. (c) Moon, V. H.: *Shock and Related Capillary Phenomena*, New York, Oxford University Press, 1938.

Seven patients were anesthetized by injecting 150 mg. of procaine hydrochloride dissolved in 3.5 cc. of cerebrospinal fluid into the subarachnoid space between the second and third lumbar vertebrae<sup>1</sup> and were placed in the Trendelenburg position (about 8 to 10 degrees). Systolic and diastolic pressures were determined by the auscultatory method at intervals of about ten minutes throughout the duration of the anesthesia and at somewhat longer intervals thereafter. The concentration of hemoglobin was determined on finger blood obtained from a freely flowing puncture wound before the induction of anesthesia,

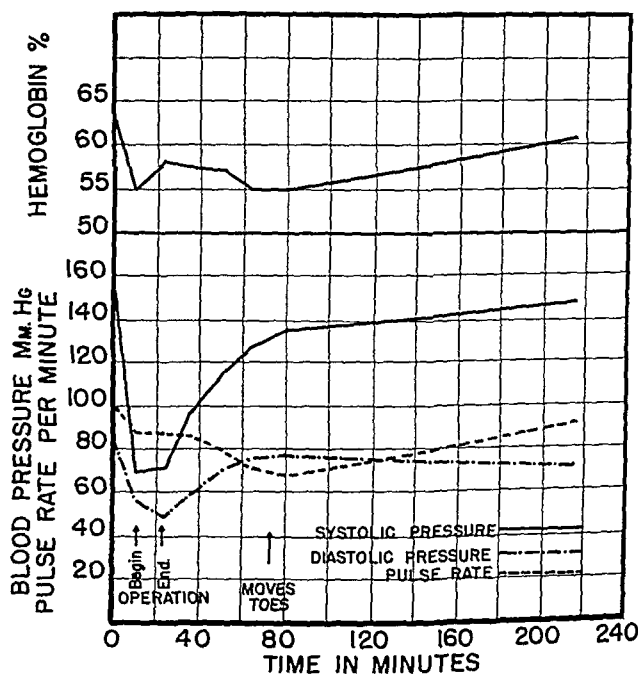


Chart 1.—Data in a typical case.

at intervals of approximately ten minutes during the anesthesia and approximately two hours after the termination of the anesthesia.

The hemoglobin determinations were done according to a modification of the method of Sanford, Sheard and Osterberg.<sup>3</sup> Blood (0.02 cc.) was placed in 10 cc. of 0.1 per cent sodium carbonate solution. The intensity of the color was determined in a photoelectric colorimeter, with a no. 978 Corning filter. A fragment of colorless fibrin was occasionally seen in the solution, but this could be easily removed by means of a capillary pipet.

The results are presented in table 1. The data on a typical case are shown graphically in chart 1.

3. Sanford, A. H.; Sheard, C., and Osterberg, A. E.: *Am. J. Clin. Path.* 3:412, 1933.



In 6 of the 7 cases the results are entirely comparable in that they show an immediate fall in the level of hemoglobin of 1 per cent to 16 per cent accompanying the fall in blood pressure and then a gradual return of both the concentration of hemoglobin and the blood pressure toward the initial level. In none of these 6 cases at any time during the observations did the value for hemoglobin reach the initial level. In the seventh case (chart 2), in which the initial value for hemoglobin was 104 per cent, there was a drop to 97 per cent at the end of six minutes. After this the concentration of hemoglobin rose gradually, until at thirty-six minutes it was 104 per cent. It reached 106 per cent

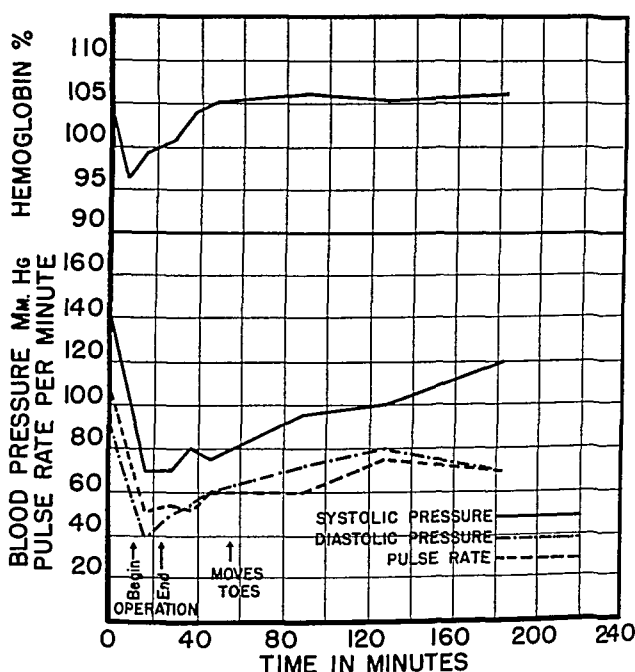


Chart 2.—Data in the case in which the content of hemoglobin rose beyond the original level.

at eighty-nine minutes and remained there at the end of one hundred and eighty-three minutes.

It is clear, then, that in the first 6 cases the values for hemoglobin indicated hemodilution rather than hemoconcentration. In the seventh case there was an initial hemodilution of about 7 per cent. The final hemoconcentration, of 2 per cent, is probably not significant.

The fall in hemoglobin may be due to pooling of the red cells somewhere off the main circulatory pathway (liver? spleen?) or to a shift of fluid into the circulatory system. To check this point, samples of blood were removed from an arm vein of each of 10 patients before the induction of spinal anesthesia, at ten minute intervals during anesthesia



and two hours after the disappearance of anesthesia. The specific gravity of the serum was determined by the falling drop method.<sup>4</sup>

The results of these determinations paralleled those of the hemoglobin determinations. There was either a slight initial fall, with gradual recovery, or no significant change.

Altogether our data indicate that the fall in blood pressure occurring with spinal anesthesia is neither preceded by nor accompanied with hemoconcentration but is, on the other hand, often accompanied with slight hemodilution, and this is evidently due to the addition of protein-free fluid to the circulating blood.

In cases of surgical shock, cardiac output falls before and after the fall in blood pressure.<sup>2a</sup> For spinal anesthesia the data available are not so complete or so satisfactory, but it is probable that the fall in blood pressure is generally accompanied with some fall in cardiac output.<sup>5</sup>

The data just given, however, suggest that the clinical significance of the diminished cardiac output in cases of surgical shock and in the presence of spinal anesthesia may not be strictly comparable. The supposed similarity in the clinical status of the patient in surgical "shock" and the patient under spinal anesthesia, therefore, deserves closer examination. A detailed comparison is given in table 2.

It is seen that of the seventeen characteristics compared, spinal anesthesia and surgical shock show complete similarity in only two, namely, the appearance of the face and the vomiting. There is partial similarity in moisture of the skin, thirst, venous pressure and mental attitude. The fall in blood pressure which has usually been considered the cardinal point of similarity between surgical shock and spinal anesthesia actually has quite different characteristics in each. In the presence of shock the fall occurs late, after compensatory vasoconstriction no longer is effectual in maintaining the normal level of blood pressure. By this time hemoconcentration is already marked. In the presence of spinal anesthesia the blood pressure falls early, and hemoconcentration does not occur. In the remaining eight characteristics analyzed in the table there is a clearcut difference between surgical shock and spinal anesthesia.

It is apparent, then, that the clinical status of a patient in surgical shock is almost entirely different from that of one under spinal anesthesia. Valid indications and contraindications for the use of spinal anesthesia must therefore be based either on an analysis of its physiologic effect or on clinical experience with its use. Reasoning based on the

4. Kagan, B. M.: *J. Clin. Investigation* **17**:369, 1938.

5. (a) Goldfarb, W.; Provisor, B., and Koster, H.: *Circulation During Spinal Anesthesia*, *Arch. Surg.* **39**:429 (Sept.) 1939. (b) Schubert, O. O.: *Acta chir. Scandinav.* (supp. 43) **78**:1, 1936.

supposed analogy between the clinical status of patients in surgical shock and that of patients under spinal anesthesia is necessarily unsound.

## SUMMARY

In 7 patients the blood pressure, pulse rate and concentration of hemoglobin were followed before, during and after spinal anesthesia, and in 10 patients the blood pressure, pulse rate and specific gravity of the serum were similarly studied.

TABLE 2.—*Comparative Analysis of Spinal Anesthesia and Surgical Shock*

	Surgical Shock	Spinal Anesthesia
Appearance of face.....	White, pale, grayish or slightly cyanotic	Same
Vomiting.....	Present	Present
Perspiration.....	Profuse	Moderate; present only in the unanesthetized areas *
Thirst.....	Marked	Slight in occasional instances*
Venous pressure.....	Low	Slightly reduced <sup>5a</sup>
Mental attitude.....	Restlessness and anxiety merging into listlessness, apathy and unconsciousness	Not characteristic; ranges in different patients from euphoria to attitudes similar to those in surgical shock *
Blood pressure.....	Normal until late and then falls	Falls early
Body temperature.....	Subnormal	Unchanged
Pulse.....	Rapid and feeble	Slowed and feeble
Temperature of skin.....	Cold all over	Elevated in anesthetized areas †
Blood pressure response to vasoconstrictor drugs	Slight and transient once blood pressure has fallen	Immediate rise; sustained after certain drugs
Oxygen consumption.....	Diminished	Unchanged ? <sup>5a,b</sup>
Leukocytosis.....	Present	Absent *
Respiration.....	Rapid	Slow *
Blood volume.....	Diminished	Unchanged <sup>5a</sup>
Hemoglobin concentration....	Increased	Slightly diminished (table 1)
Prognosis.....	Grave if untreated	Good if untreated *

\* Unpublished data.

† Scott, W. J. M., and Morton, J. J.: Sympathetic Activity in Certain Diseases, Especially Those of Peripheral Circulation, *Arch. Int. Med.* 48:1065 (Dec.) 1931.

The data indicate that the value for hemoglobin and the specific gravity of the serum fall slightly with the onset of the anesthesia and return gradually to their initial level.

The absence of hemoconcentration suggested a reexamination of the supposed similarity of the clinical status of patients in surgical shock to that of patients under spinal anesthesia.

The characteristics of the clinical status of patients in the two states are fundamentally different.

Reasoning concerning indications or contraindications for spinal anesthesia, based on the supposed analogy between its effects and the state of "surgical shock," is not valid.

## CARCINOMA OF THE LARGE INTESTINE

REVIEW OF FOUR HUNDRED AND SIXTEEN AUTOPSY RECORDS

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Many papers are to be found in the literature dealing with problems of malignant tumor of the colon. A vast amount of material has accumulated on all phases of the subject, especially in the hospital records pertaining to mortality, morbidity and treatment.

It occurred to me that it would be interesting to take a group of cases in which autopsy had been performed for study of the nature of the lesion at the time, making an effort to analyze some of the difficulties that hedge about clinical recognition of the disorder. All of the patients reported on in this review came to necropsy in the department of pathology at the University of Minnesota between January 1910 and July 1937 because of carcinoma of the large bowel.

That this material represents a fair sample of the general population is attested by the fact that in 1927 it was found that 19 per cent of the deaths in the city of Minneapolis were included in the necropsy experience of the department of pathology.<sup>1</sup>

It is the purpose of this paper to scrutinize the clinicopathologic data found in the autopsy records and to evaluate them in terms of present day opinion.

### SOURCE OF MATERIAL

Four hundred and sixteen records of carcinoma of the large intestine and of the rectal canal were collected from 26,798 autopsy records. The examinations were made by numerous pathologists with a variable range of experience, from the head of the department and his associates to the junior members and volunteer assistants.

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Abridgment of a thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

1. Bell, E. T.: Circumstances That Influence the Obtaining of Necropsies, *J. A. M. A.* 90:896 (March 24) 1928.

In reviewing the records and tabulating the information contained in each autopsy account, considerable assistance was afforded by reference to the abstract record sheet devised by Hayden and Shedden.<sup>2</sup>

#### STATISTICAL DATA

A. *Incidence*.—1. Sex: The sex incidence in 26,798 necropsies performed during the period under consideration was 17,488 males and 9,310 females, or a ratio of 1.86 to 1. The sex ratio for the whole and that for carcinoma of the large bowel were essentially the same, for of the 416 patients with malignant tumor of the large intestine 266 (63.9 per cent) were males and 150 (36.1 per cent) were females, the ratio being 1.77 to 1. In this series the females with carcinoma of the large intestine comprised 18.2 of every thousand females, while the males with the same condition comprised 15.2 of every thousand males, on whom autopsy was performed. Numerically there were more males with carcinoma of the colon because more autopsies were performed on patients of this sex, but in percentage of total autopsies there was no significant difference.

2. Age: The average age was found to be 50 years and 6 months. Approximately 10 per cent of all patients were under 35 years of age, but the greatest frequency was in the fifth, sixth and seventh decades, the seventh showing the highest incidence for each sex and for the combined sexes.

Harding and Hawkins<sup>3</sup> reported the greatest age incidence in their series to be in the fifth and sixth decades. A predominance in the so-called cancer age, the fifth, sixth and seventh decades—the highest incidence being in the fifth decade—was observed by Raiford<sup>4</sup> in a group of 511 patients with cancer of the colon and of the rectum admitted to the Johns Hopkins Hospital during the first forty-two years after its wards opened in 1889.

3. Site: The rectum, the sigmoid flexure and the cecum were found to be the most common colonic sites of cancer; however, 67.2 per cent of all the carcinomas of the colon were located in the distal portion.

The distribution of colonic cancers by anatomic sites as noted by eleven observers is shown in table 1. About one fourth of the tumors were located in the cecum and ascending colon, one fifth in the midcolon and approximately half in the descending colon and sigmoid flexure.

Carcinoma of the rectum is more common in males than in females. The autopsy material in the present review showed that the percentage

2. Hayden, E. P., and Shedden, W. M.: Carcinoma of the Rectum: Study of Three Hundred and Three Cases, *Surg., Gynec. & Obst.* **51**:783 (Dec.) 1930.

3. Harding, W. G., and Hawkins, F. D.: Post Mortem Observations of One Hundred and Eighteen Carcinomas of the Large Bowel, *Am. J. Cancer* **17**:434 (Feb.) 1933.

4. Raiford, T. S.: Carcinomas of the Large Bowel: I. The Colon, *Ann. Surg.* **101**:863 (March) 1935.

of males with carcinoma of the rectum was 71.2 and that of females 28.8. Raiford,<sup>5</sup> in a series of 319 tumors of the rectum, observed a similar selection, with approximately 74 per cent males and 26 per cent females.

Dr. William Peyton, who assisted greatly in this study, pointed out that an autopsy series like this would eliminate the cured lesions and make the incidence of the location most favorable for cure low and that of the less favorable locations higher.

TABLE 1.—*Location of Colonic Cancer*

Series	Cases	Cecum and Ascending Colon, Percentage	Transverse Colon and Flexures, Percentage	Descending Colon and Sigmoid Flexure, Percentage
Raiford *	182	38	23	39
Prickman, L. E.: The Blood Picture with Cancer and Other Conditions of the Colon, Thesis, University of Minnesota Graduate School, March 1937	231	36	24	40
Behrend, M.: Carcinoma of Colon; Treatment Depending on Location of the Lesion, Surg., Gynec. & Obst. <b>65</b> :505 (Oct.) 1937	98	18	20	62
Judd, E. S.: A Consideration of Lesions of the Colon Treated Surgically, South. M. J. <b>17</b> :75 (Feb.) 1924	625	26	20	54
Lockhart-Mummery, J. P.: Diseases of the Rectum and Colon, Baltimore, William Wood & Company, 1934, p. 352	560	23	22	55
Erdman, J. F.: Malignancy of the Colon, with Especial Reference to Those of the Rectal Zone, Am. J. Digest. & Nutrition <b>1</b> :881 (Feb.) 1935	119	16	15	69
Graham, R. R.: Carcinoma of the Colon, Am. J. Digest. Dis. & Nutrition <b>1</b> :584 (Oct.) 1934	86	38	14	48
Winkle, D. P. D.: Cancer of the Colon: Its Surgical Treatment, Lancet <b>1</b> :65 (Jan. 13) 1934	101	20	17	64
Lahey <sup>20</sup>	73	26	20	54
Rosser, O.: Diagnostic Criteria of Colonic Cancer, J. A. M. A. <b>106</b> :109 (Jan. 11) 1936	100	32	19	49
Present series	281	33	16	51

*B. Problem of Delay in Diagnosis and Treatment.*—Many cancers are curable if treated in time. To reduce the delay before treatment is important in reducing the mortality from the disease. For this the initial responsibility lies with the patient; however, equally important are a correct diagnosis and early institution of adequate therapy on the part of the first physician consulted. The delays encountered due to the inability of the physician to make a correct and early diagnosis of cancer are not confined to internal neoplasms, of which diagnosis is difficult, but are encountered in cases of carcinoma of the breast, of the uterine cervix, of the lower part of the rectum and of the oral cavity, in which diagnosis is relatively easy and cure possible.

5. Raiford, T. S.: Carcinoma of the Large Bowel: II. The Rectum, Ann. Surg. **101**:1042 (April) 1935.

Rankin<sup>6</sup> found that the average patient is aware of some of the characteristic symptoms of colonic cancer approximately eleven months prior to seeking medical advice.

In an analysis of 1,000 cases of cancer reported by Pack and Gallo,<sup>7</sup> delay in treatment was due to the patient alone in 44.3 per cent, to the patient and the physician in 18 per cent and to the physician alone in

TABLE 2—*Distribution of Carcinoma of the Large Intestine by Sex and Decade*

Site of Lesion	Decade										All Age-
	1	2	3	4	5	6	7	8	9		
Males											
Cecum and ascending colon		1	1	5	12	12	14	11	1	57	
Hepatic flexure...					3	1	2			6	
Transverse colon					1	2	4	1		8	
Splenic flexure..					1	1	7	2		11	
Proximal part of colon..		1	1	5	17	16	27	14	1	82	
Descending colon				1	1			1		3	
Sigmoid flexure		1		6	6	9	19	19	1	61	
Rectosigmoid		1	1		2	7	8	3	2	24	
Rectum			1	6	15	32	22	20		96	
Distal part of colon		2	2	13	24	48	49	43	3	184	
Large intestine		3	3	18	41	64	76	57	4	266	
Females											
Cecum and ascending colon	1	1		1	4	5	15	8	2	37	
Hepatic flexure				1	2	1	1	1		6	
Transverse colon			1		2	2	2			7	
Splenic flexure			1	1	1	1			1	5	
Proximal part of colon	1	1	2	3	9	9	18	9	3	50	
Descending colon				1		3	2			6	
Sigmoid flexure			1	1	6	12	14	8	2	44	
Rectosigmoid..		1	1	1	3	7	11	4	2	30	
Rectum			2	3	7	11	11	3	2	39	
Distal part of colon			3	6	14	26	30	12	4	95	
Large intestine	1	1	5	9	23	35	48	21	7	150	
Combined Sexes											
Cecum and ascending colon	1	2	1	6	16	17	29	19	3	94	
Hepatic flexure				1		2	1	1		12	
Transverse colon			1		3	4	6	1		15	
Splenic flexure			1	1	2	2	7	2	1	16	
Proximal part of colon	1	2	3	8	26	25	45	23	4	137	
Descending colon				2	1	3	2	1		9	
Sigmoid flexure		1	1	7	12	21	33	27	3	105	
Rectosigmoid...		1	1	1	3	7	11	4	2	30	
Rectum			3	9	22	43	33	23	2	135	
Distal part of colon		2	5	19	38	74	79	55	7	279	
Large intestine	1	4	8	27	64	99	124	78	11	416	

17 per cent. No delay was noted by these authors in 20.7 per cent of cases. A delay of three months and over from the discovery of symptoms to a visit to the physician was regarded as undue delay. These authors concluded that, together with the campaign to educate the public, further effort should be made to train physicians in early diagnosis and treatment.

6. Rankin, F. W. Present-Day Surgical Treatment of the Rectum and Rectosigmoid, *Minnesota Med.* **16**:23 (Jan) 1933

7. Pack, G. T., and Gallo, J. S.: The Culpability for Delay in the Treatment of Cancer, *Am J. Cancer* **33**:443 (July) 1938

Many authors have mentioned the difficulties of differential diagnosis. Schwartz and Berman,<sup>8</sup> Rosser,<sup>9</sup> Bloodgood,<sup>10</sup> Harding and Hawkins,<sup>3</sup> Ewing,<sup>11</sup> Horgan,<sup>12</sup> Mallory,<sup>13</sup> Dixon,<sup>14</sup> Jordan<sup>15</sup> and de Tarnowsky and Sarma<sup>16</sup> stated that the failure of the family physician to be alert for the possibility of cancer is no doubt responsible for the tardiness with which most patients with carcinoma of the large intestine reach the surgeon.

In this series the average duration of symptoms before diagnosis was thirteen months for lesions in the right side of the colon; twelve and one-half months for lesions in the transverse and descending colon, and fourteen months for lesions in the sigmoid flexure. Simpson,<sup>17</sup> in a clinical series of 120 cases of cancer of the colon, found that the average duration of symptoms for lesions in the right side of the colon was eleven months; for those in the transverse and descending colon, twelve months, and for those in the sigmoid flexure, fourteen months.

*C. The Confusing Clinical Picture.*—The confusing clinical picture produced by malignant neoplasms of the large intestine may result from the fact that the location of the tumor, its rate of growth, its progressive nature and certain secondary systemic conditions in themselves not infrequently represent well established clinical entities on cursory examination and also from the fact that patients of the age groups affected are prone to many diseases which are more likely to occur to the physician than is cancer of the colon.

Table 3 shows the various erroneous diagnoses made and the interval in months from diagnosis to death in 115 cases of carcinoma of the large intestine. In some instances only the type of operation was recorded,

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8. Schwartz, J., and Berman, H.: Gynecological Features of Carcinoma of the Large Bowel, *Am. J. Obst. & Gynec.* **36**:85, 1938.

9. Rosser, C.: Diagnosis and Management of Rectal Cancer, *Southwestern Med.* **15**:464 (Oct.) 1931.

10. Bloodgood, J. C.: Cancer of the Colon and Rectum: Personal Experiences from 1892 to 1932, *Ann. Surg.* **95**:590 (April) 1932.

11. Ewing, M. Q.: Carcinoma of Colon, *New Orleans M. & S. J.* **86**:470 (Jan.) 1934.

12. Horgan, J.: Early Diagnosis of Cancer of the Rectum and Recto-Sigmoid, *M. Ann. District of Columbia* **2**:197 (Sept.) 1933.

13. Mallory, W. J.: Medical Aspects of Carcinoma Colon, *J. M. Soc. New Jersey* **30**:496 (July) 1933.

14. Dixon, C. F.: Carcinoma of the Right Half of the Colon: Diagnosis and Treatment, *New York State J. Med.* **38**:1262 (Oct. 1) 1938.

15. Jordan, S. M.: Diagnosis of Carcinoma of the Colon, *S. Clin. North America* **13**:569 (June) 1933.

16. de Tarnowsky, G., and Sarma, P. F.: Carcinoma of the Colon and Rectum, *S. Clin. North America* **13**:1221 (Oct.) 1933.

17. Simpson, W. C.: The Mural Penetration of the Cancer Cell in the Colon, Thesis, University of Minnesota Graduate School, March 1938.

rather than the clinical diagnosis for which operation was performed. Not included in this table were the instances in which an operation was performed on the basis of an erroneous diagnosis but in which the correct diagnosis was established during the operation.

That lesions of the distal part of the colon may lead to a diagnosis of appendicitis, as well as to a diagnosis resulting in cholecystectomy, was noted.

TABLE 3.—*Erroneous Clinical Diagnoses and Time When Made in One Hundred and Fifteen Cases of Carcinoma of the Large Intestine (According to Site)*

Site of Lesion and Diagnosis	Number of Diagnoses	Months Prior to Autopsy
<b>Cecum and ascending colon:</b>		
Anemia.....	1	2
Anemia, pernicious.....	4	36-9-12-00
Appendicitis.....	3	5-7-12
Appendectomy.....	2	12-24
Appendical abscess.....	1	16
Cancer of prostate.....	1	1
Cancer of sigmoid flexure.....	1	2
Cancer of stomach.....	1	12
Cellulitis.....	1	1
Cholecystitis.....	3	12-4-24
Chronic intestinal obstruction.....	1	4
Colitis.....	2	24-8
Dyspepsia.....	1	7
Endothelioma of pleura.....	1	4
Hernia.....	1	2
Hernia, internal.....	1	2
Hernia, strangulated.....	1	1
Hodgkin's disease.....	1	7
Intestinal intoxication.....	1	1
Nephrolithiasis.....	1	2
Neurosis.....	1	12
Peptic ulcer.....	1	18
Rectal polyp.....	1	24
Tuberculous peritonitis.....	1	12
Tumor.....	1	2
Tumor, retroperitoneal.....	1	12
Tumor, uterine.....	1	8
	36	Average, 11
<b>Hepatic flexure:</b>		
Anemia.....	1	28
Appendectomy.....	1	18
Prostatism.....	1	?
	3	Average, 15
<b>Transverse colon:</b>		
Anemia.....	2	10-48
Cancer of stomach.....	1	8
Tumor, abdominal wall.....	1	12
Tumor, ovarian.....	1	7
	5	Average, 17
<b>Splenic flexure:</b>		
Cancer of esophagus.....	1	3
Heart disease.....	1	2
Hypochondriasis.....	1	42
Peptic ulcer.....	1	3
	4	Average, 12
<b>Descending colon:</b>		
Anemia.....	1	16
Appendectomy.....	1	3
	2	Average, 9



TABLE 3.—*Erroneous Clinical Diagnoses and Time When Made in One Hundred and Fifteen Cases of Carcinoma of the Large Intestine (According to Site)—Continued*

Site of Lesion and Diagnosis	Number of Diagnoses	Months Prior to Autopsy
Sigmoid flexure:		
Appendicitis.....	1	9
Appendectomy.....	2	11-60
Cancer of liver.....	2	15-7
Cancer of stomach.....	1	8
Cholecystectomy.....	1	7
Colitis.....	1	24
Constipation.....	2	36-12
Diarrhea.....	3	24-12-?
Dyspepsia.....	1	12
Hemorrhoids.....	2	12-8
Heart disease.....	1	?
Hodgkin's disease.....	1	?
Hysterectomy.....	1	12
Mesenteric thrombosis.....	1	1
Peritonitis.....	2	12-8
Polyposis of colon.....	1	60
Tumor of pancreas.....	1	5
Tumor of uterus.....	1	4
Ulceration of rectum.....	1	12
	26	Average, 14
Rectosigmoid		
Diarrhea.....	1	3
Hemorrhoids.....	1	5
Hemorrhoidectomy.....	1	4
Hysterectomy.....	1	24
Prostatism.....	2	18-?
	6	Average, 9
Rectum:		
Anemia, pernicious.....	1	9
Appendicitis.....	1	1
Appendectomy.....	1	3
Cancer of bladder.....	1	4
Cancer of gallbladder.....	1	72
Cancer of liver.....	1	5
Cholecystitis.....	1	36
Cirrhus liver.....	1	9
Dysentery.....	2	15-6
Fistula in ano.....	2	24-12
Hemorrhoids.....	5	36-12-2-12-12
Hemorrhoidectomy.....	5	3-5-5-6-12
Hernioplasty.....	1	24
Heart disease.....	3	2-2-24
Inflammation of bowel.....	1	36
Menorrhagia.....	1	?
Prostatism.....	1	6
Stricture of rectum.....	1	2
Tuberculosis, pulmonary.....	1	2
Ulceration of rectum.....	2	3-6
	33	Average, 12

Priestley and Bargaen<sup>18</sup> reported a series of 100 cases of carcinoma of the large intestine, in which 15 per cent of the patients had been subjected to appendectomy; Brindley<sup>19</sup> reported 18 per cent of appendectomies in a similar series.

In the present series 16.6 per cent of the incorrectly diagnosed cecal lesions were diagnosed as appendicitis (1 as appendical abscess), while 8.3 per cent were diagnosed as cholecystitis. But more important

18. Priestley, J. T., and Bargaen, J. A.: Early Diagnosis of Carcinoma of the Large Intestine, *Am. J. Surg.* 22:515 (Dec.) 1933.

19. Brindley, G. V.: Symptomatology and Diagnosis of Cancer of the Large Bowel, *Texas State M. J.* 23:325 (Sept.) 1927.

was the fact that recent hemorrhoidectomies had been performed in 5.2 per cent of cases of carcinoma of the rectum and of the rectosigmoid juncture without discovery of the carcinoma. Pannett<sup>20</sup> stated the belief that the occurrence of hemorrhoids in association with carcinoma of the rectum may be due to the growth of tumor above blocking the venous channels below.

Anemia was diagnosed in 10 instances; 1 patient was treated for five years for pernicious anemia. A patient in whose case a diagnosis of hypochondriasis had been made was treated symptomatically for three years. Deaver<sup>21</sup> indicated the importance of secondary anemia in cases of cancer of the colon and mentioned that proximal colonic lesions may simulate pernicious anemia.

A summary of the clinical diagnoses in the present study indicated that a correct diagnosis had been made in 35 per cent of 371 cases of carcinoma of the colon; in 4 per cent the lesions were asymptomatic up to the time of acute obstruction; in 7 per cent they were diagnosed as intestinal obstruction (cause undetermined); in 31 per cent they were incorrectly diagnosed; in 3.8 per cent they were not diagnosed, and in 19 per cent they could not be classified because of insufficient data.

Stebbins and Burke<sup>22</sup> reported on 295 cases of carcinoma of the colon and rectum and noted 125 correct diagnoses (42.3 per cent), only 83 of 163 rectal cancers (52 per cent) being correctly diagnosed, although over 82 per cent of the tumors were within reach of the index finger.

In the present series of 119 rectal cancers, 48 per cent were correctly diagnosed. This is the highest percentage of correct diagnoses for any anatomic site. The distal portion of the colon was associated with a higher percentage of correct diagnoses (39.9) than was the proximal portion (25.2).

*D. Symptoms.*—The first symptoms of a malignant neoplasm of the large intestine are usually due to some effect of the tumor itself. The lesions are less likely to be confused with other diagnostically possible conditions in obscure cases if one bears in mind the probability of a carcinoma of the large intestine and employs such diagnostic procedures as will aid in excluding such a lesion. Malignant lesions of the large bowel are often silent until they are of considerable size.

Symptoms vary according to the character and location of the lesion in the colon. When the lesion occurs in the region of the cecum, symptoms of appendicitis may appear. The same may be said of lesions in

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20. Pannett, C. A.: Cancer of the Colon, *Brit. M. J.* **1**:104 (Jan. 2) 1926.

21. Deaver, J. B.: Surgery of the Right Half of the Colon, *Ann. Surg.* **80**:439 (Sept.) 1924.

22. Stebbins, G. S., and Burke, M.: Cancer of the Rectum and Colon, *Am. J. Surg.* **37**:437 (Sept.) 1937.

the ascending colon and in the hepatic flexure. Only when the abdomen is opened is the true cause of the condition revealed. Lesions in the flexures of the colon may give rise to signs and symptoms of disease of the gallbladder, peptic ulcer, heart disease, renal neoplasm or functional alteration of the stomach and intestine.

Fansler and Anderson<sup>23</sup> said that the symptoms to emphasize are not those which indicate that a cancer is surely present but those which indicate that a cancer may possibly be present. There are no specific signs that indicate the presence of such a dangerous lesion.

With the distal portion of the colon, increasing constipation, borborygmus, mild intestinal colic, flatulence or gurgles and rumblings in the bowel, when present, should lead one to consider the reason for a change in intestinal habit.

"Rumbling of gas" in the bowel was noted in this series by 26 patients, early in the disease by 19; 16 of them had lesions in the distal part of the colon. Mucus in the feces was reported by 21 patients, 12 of them with early involvement; all but 1 had lesions in the distal portion of the colon. Vague abdominal distress was noted by 16 patients; 10 of them described it as "intestinal indigestion," while 6 called it "dyspepsia."

1. Change of Intestinal Habit: Of the 353 patients on whom data were available concerning a change of intestinal habit, 62.3 per cent presented a definite change.

2. Diarrhea: This symptom occurred in 44 patients early in the course of the disease and in 13 patients in the late stages. Of 57 patients reporting diarrhea, 24 had carcinoma of the rectum; of 44 with diarrhea as an early symptom, 15 had carcinoma of the proximal portion of the colon. There were 309 who did not mention diarrhea as a symptom.

3. Constipation, Alone or Alternating with Diarrhea: This is a common early symptom mentioned in many textbooks.<sup>24</sup> Swinton<sup>25</sup> reported the history of alternating diarrhea and constipation for less than 1 of 4 patients with carcinoma of the rectum. In the material studied, 10 of 371 (2.7 per cent) patients presented a history of alternating diarrhea and constipation; however, no mention of this symptom was made by 361. Lahey<sup>26</sup> reported that 8 per cent of a series of 100

23. Fansler, W. A., and Anderson, J. K.: *Carcinoma of the Colon*, Nebraska M. J. **19**:361 (Oct.) 1934.

24. Cecil, R. L.: *Textbook of Medicine*, ed. 3, Philadelphia, W. B. Saunders Company, 1934, p. 798. Musser, J. H.: *A Practical Treatise on Medical Diagnosis*, ed. 5, Philadelphia, Lea Brothers & Company, 1904, p. 1065.

25. Swinton, N. W., and Higginbotham, J.: *Diagnosis of Carcinomas of Colon and Rectum*, S. Clin. North America **18**:733 (June) 1938.

26. Lahey, F. H.: *Carcinoma of the Colon*, Am. J. Surg. **22**:64 (Oct.) 1933.

patients with carcinoma of the colon gave a history of alternating diarrhea and constipation.

4. Nausea and Vomiting: In a series of 261 patients with carcinoma of the large intestine, no data on these symptoms were available. Lesions of the proximal portion of the colon, especially the cecum, were accompanied with nausea in 19 of 20 cases in which the symptom was recorded. In the distal portion of the colon, lesions of the sigmoid flexure were more likely to produce this symptom (50 per cent) than were all carcinomas in other colonic sites combined. Vomiting was complained of by 42 of 50 patients with carcinoma of the proximal portion of the colon and by 53 of 60 with lesions of the distal portion.

5. Painful Defecation: Painful defecation occurred in 32 instances. As an early symptom it was noted by 30 patients, 23 of whom had a carcinoma of the rectum, 2 a lesion in the rectosigmoid juncture, 4 a lesion in the sigmoid flexure and 1 a lesion in the splenic flexure.

6. Change in Character of Stool: This was noted by 13 patients; 1 had a carcinoma in the sigmoid flexure of the colon, 3 in the rectosigmoid portion and 9 in the rectum.

7. Loss of Weight: Loss of weight is nearly always suggestive of cancer when associated with abdominal symptoms in a patient past middle age. This symptom, when present, occurred late in 85 per cent of the cases; hence one should not be misled by the robust or healthy appearance of a patient with one or more of the previously mentioned symptoms if the diagnosis of such a lesion is to be established early.

8. Constipation or Obstipation: This type of symptom was present early in most cases in which there was any degree of colonic obstruction. It was noted and recorded in association with 29.8 per cent of 121 lesions of the proximal portion of the colon and with 44.8 per cent of 232 malignant lesions of the distal portion. In 39.6 per cent of 353 patients constipation amounted to a definite dysfunction. Obstipation occurred in 6.8 per cent of 24 cases; 20 of the lesions were in the distal part of the colon. The data were complete in 353 of a possible 371 cases.

9. Obstruction: In most cases of malignant disease of the right half of the colon obstruction plays a minor role. In this series 43 per cent of the patients with proximal colonic lesions had neither symptoms nor findings suggesting obstruction; only 13 per cent of patients with distal colonic lesions were free of obstructive changes. Complete obstruction was found with 23.1 per cent of proximal colonic lesions, while 33.2 per cent of 232 carcinomas of the distal portion of the colon caused obstruction.

10. Bleeding: The history of gross bleeding from the bowel demands immediate investigation for carcinoma of the large intestine. Frank hemorrhage was an early symptom with 6.9 per cent of 128 lesions in the distal part of the colon; 18.7 per cent of 61 proximal colonic lesions pre-

sented evidence of hemorrhage. Gross blood or occult blood was noted with 40.7 per cent of all lesions; with 8.6 per cent bleeding was never demonstrable either grossly, microscopically or by chemical tests. No data were available on 49 per cent of the total of 371.

11. Hemorrhoids: It is interesting to note that the coincidental clinical diagnosis of hemorrhoids was made in 36 instances (9.44 per cent); however, hemorrhoids was given as the initial diagnosis (table 3) in 14.

12. Anemia: The degree and type of anemia found in patients with carcinoma of the colon and especially carcinoma of the cecum have attracted the attention of numerous investigators since Mayo<sup>27</sup> made the observation that "patients with a cecal tumor often have a profound anemia without any apparent good reason for it." Prickman<sup>28</sup> demonstrated a correlation between the degree of anemia and the size of carcinomas located in the cecum. Many patients with such lesions have been treated for primary anemia.

For 63 patients with carcinoma in the proximal portion of the colon the initial value for hemoglobin and the erythrocyte count averaged respectively 63.26 per cent (Sahli) and 3,700,000 erythrocytes per cubic millimeter of blood, while 112 patients with carcinoma in the distal portion of the colon had an average level of hemoglobin of 69.3 per cent and an average red cell count of 3,870,000 per cubic millimeter. Prickman, in 303 cases of carcinoma of the colon, found that anemia was more marked with malignant disease of the cecum and ascending colon.

13. Pain (table 4): Pain or discomfort frequently was the presenting complaint, varying from general distress due to gas to pain localized over the site of the lesion. Localized pain on the right side was often found to indicate a lesion in the proximal portion of the colon. There were 89 patients, 34.5 per cent of 258, who complained of pain at the site of the lesion; 27.9 per cent complained of general abdominal distress. Seven per cent of 258 patients did not complain of pain.

14. Palpable Tumor: Stebbins and Burke,<sup>22</sup> reporting a series of 295 cases of carcinoma of the rectum and colon, stated that a tumor was palpable in 180.

In the autopsy material studied, palpable tumors in the rectosigmoid portion of the colon were infrequent, only 2 of 29 lesions being palpable. Such lesions, however, are readily visualized by the use of a proctoscope or a sigmoidoscope. Lesions located in the proximal portion of the colon were found to be more often palpable than were those in the distal portion. Three of 10 carcinomas in the splenic flexure were palpable.

27. Mayo, W. J.: Tumors of the Cecum, *Journal-Lancet* 2:523 (Dec. 15) 1909.

28. Prickman, L. E.: The Changes in the Blood Picture with Carcinoma of the Colon, *Proc. Staff Meet., Mayo Clin.* 2:80 (April 12) 1927.

E. *Diagnostic Methods*.—1. Biopsy: Biopsy is the most important diagnostic procedure in cases in which the gross diagnosis of the lesion is uncertain but suspected. However, biopsy specimens are sometimes taken in such a way that even though cancer is present, it is not included in the specimen. Use of such an improperly removed biopsy specimen endangers the patient's welfare. The pathologist also may be led into error if he takes only one or two sections from a block of tissue which requires a series of sections from various parts of the block.

There were 39 biopsies reported for this series, in only 3 of which an incorrect diagnosis was made by the pathologist. Such an error is not impressive in itself unless one considers the undue importance usually attached to this method of diagnosis. No single procedure should carry the full responsibility for diagnosis; the results of all should be integrated with the clinical picture.

TABLE 4—*Incidence of Pain in Cases of Carcinoma of the Large Intestine According to Site of Lesion and Location of Pain*

Site of Lesion	Symptom Re corded	No Pain	Pain at Site of Lesion	Epi- gastrie Pain	General Abdom- inal Pain	Colic (Cramps)	Rectal Pain	Sacral Pain	Back ache
Cecum and ascending colon	68	5	31	7	18	7	..		
Hepatic flexure ....	8	3	1	1	2	1	..		
Transverse colon.. ..	10		4	4	4	2			
Splenic flexure. .. ..	10	1	5	1	1	2			
Proximal part of colon..	56	9	37	13	25	12	..	..	
Descending colon .	6	..	3	1	1	1			
Sigmoid flexure	70	4	15	5	21	24	1		
Rectosigmoid	19	1	2		12	3		1	
Rectum. . . . .	67	4	32	5	13	7		1	3
Distal part of colon	162	9	52	11	47	15	1	2	5
Large intestine	258	18	89	24	72	47	1	2	5

2. Roentgen Examination (table 5): The literature is replete with indications for certain diagnostic procedures. Weber<sup>29</sup> recommended that any patient with a change in intestinal habit evidenced by irritability, mucus, diarrhea, alternating periods of constipation and diarrhea or localized pain and tenderness which do not tend to disappear, not to mention tumefaction, anemia and obstruction, should have a thorough roentgen investigation of the intestinal tract.

In this series 97 roentgen studies of the colon were reported in the autopsy records. Of these the diagnoses in 84.5 per cent were correct; in 5.2 per cent they were uncertain, and in 10.3 per cent they were incorrect.

In this connection it could be mentioned that the progressive nature of the lesion necessarily indicates the repeated use of roentgen examination at intervals in keeping with the clinical progress of the disease.

F. *Pathologic Changes*.—1. Circumferential Involvement (table 6): The degree of involvement is selected in this series, as a completely

29. Weber, H. M.: Carcinoma of the Colon: Its Roentgenologic Manifestations and Differential Diagnosis, *Am J. Cancer* **17**:321 (Feb.) 1933

encircling lesion was more often described in detail by the pathologist than was a lesion of less significance. This is especially evident with lesions of the cecum. Fifteen such lesions were described, 12 of which involved the entire bowel wall in a site where completely obstructing

TABLE 5.—*Result of Roentgen Diagnosis in Ninety-Six Roentgen Studies of Carcinoma of the Large Intestine*

Site of Lesion	Total Cases	Diagnoses Recorded		Correct Diagnoses		Uncertain Diagnoses		Incorrect Diagnoses	
		Num-ber	Per-cent-age	Num-ber	Per-cent-age	Num-ber	Per-cent-age	Num-ber	Per-cent-age
Cecum and ascending colon...	83	32	38.6	29	90.6	1	3.1	2	6.3
Hepatic flexure.....	10	2	20.0	1	50.0	..	....	1	50.0
Transverse colon....	14	4	28.6	2	50.0	..	....	2	50.0
Splenic flexure.....	16	6	37.5	5	83.3	1	16.7	..	....
Proximal part of colon....	123	44	35.7	37	84.1	2	4.5	5	11.4
Descending colon.....	7	2	28.6	2	100.0	..	....	..	....
Sigmoid flexure.....	93	35	37.6	29	83.0	2	5.6	4	11.4
Rectosigmoid.....	29	8	27.3	7	87.5	1	12.5	..	....
Rectum.....	119	8	6.7	7	87.5	..	....	1	12.5
Distal part of colon ....	248	53	21.4	45	84.8	3	5.7	5	9.5
Large intestine.....	371	97	26.1	82	84.5	5	5.2	10	10.3

TABLE 6.—*Circumferential Involvement of the Wall of the Large Intestine by Carcinoma as Found in Four Hundred and Sixteen Autopsy Records*

Site of Lesion	Total Cases	Circumferential Involvement							
		Cases		360 Degrees		270 Degrees		180 Degrees or Less	
		Num-ber	Per-cent-age	Num-ber	Per-cent-age	Num-ber	Per-cent-age	Num-ber	Per-cent-age
Cecum and ascending colon..	94	15	16.0	13	86.6	1	6.7	1	6.7
Hepatic flexure.....	12	5	41.7	4	80.0	1	20.0	..	....
Transverse colon....	15	4	26.8	2	50.0	1	25.0	1	25.0
Splenic flexure....	16	4	25.0	3	75.0	1	25.0	..	....
Proximal part of colon.....	137	28	20.4	22	78.6	4	14.3	2	7.2
	9	..	....	..	....	..	....	..	....
	103	35	33.3	27	77.2	6	17.1	2	5.7
	30	8	26.7	7	87.5	1	12.5	..	....
Rectum.....	135	52	38.4	39	75.0	5	9.6	8	15.4
Distal part of colon..	279	95	34.1	73	76.8	12	12.6	10	10.6
Large intestine. ....	416	123	29.6	95	77.2	16	13.0	12	9.8

lesions are not the rule. A description of the circumferential involvement of the wall of the colon was recorded for 29.6 per cent of carcinomas of the colon.

Miles<sup>30</sup> estimated that it requires six months for a rectal or colonic carcinoma of average malignancy to traverse one fourth of the circumference and that about the same time is required for lateral extension to affect the mucosa or the muscular layer.

30. Miles, W. E.: Pathology of Spread of Cancer of Rectum, and Its Bearing upon Surgery of Cancerous Rectum, Surg., Gynec. & Obst. 52:350 (Feb., no. 2A) 1931.

2. Metastases and Sites of Secondary Tumor: Visceral metastases may take place by lymphatics, by neoplastic emboli breaking off into the portal circulation<sup>31</sup> or by direct extension into the surrounding organs. Metastases had taken place in 57 per cent of the cases in this study.

TABLE 7.—*Distribution of Secondary Tumor Sites in Two Hundred and Forty Cases of Carcinoma of the Large Intestine*

Site of Secondary Lesion	Large Intestine	Cecum and Ascending Colon	Hepatic Flexure	Transverse Colon	Splenic Flexure	Descending Colon	Sigmoid Flexure	Recto-sigmoid	Rectum
Cases with metastases	240	56	7	10	7	4	54	16	86
Location of metastases:									
Liver.....	136	27	4	7	4	3	29	13	49
Regional nodes.....	101	25	5	3	3	2	28	4	31
Peritoneum.....	49	14	1	2	3	1	8	3	17
Pararectal nodes.....	36	3	..	..	..	..	1	1	31
Lungs.....	35	6	1	1	..	1	5	3	15
Intestine.....	30	11	..	..	1	..	6	3	9
Bladder.....	25	1	..	..	..	..	5	1	18
General abdominal.....	19	7	1	1	..	..	7	..	3
Inguinal nodes.....	13	2	..	..	1	..	4	1	5
Omentum.....	13	9	..	..	..	..	3	1	..
Aortic nodes.....	12	1	..	..	..	1	5	1	4
Kidney.....	12	5	..	..	1	..	3	1	2
Mesentery.....	12	3	..	1	2	..	5	1	..
Spleen.....	12	3	..	..	2	..	3	..	4
Adrenal gland.....	8	..	1	..	..	1	2	..	4
Abdominal wall.....	7	6	..	..	..	..	..	2	1
Pancreas.....	7	2	..	..	..	..	1	..	2
Prostate.....	7	..	..	..	..	..	..	..	7
Brain.....	6	..	..	1	..	1	3	..	1
Ovary.....	6	..	1	..	..	..	2	..	3
Uterus.....	6	..	..	..	..	..	2	1	..
Diaphragm.....	4	2	..	..	1	..	1	..	..
Stomach.....	4	..	..	1	2	..	1	..	2
Bone.....	3	1	..	..	..	..	..	..	2
Gallbladder.....	3	..	1	..	..	..	..	..	..
Mediastinal nodes.....	3	3	..	..	..	..	..	..	1
Skin.....	3	1	..	1	..	..	..	..	..
Iliacus muscle.....	2	2	..	..	..	..	..	..	..
Incisional.....	2	1	..	1	..	..	..	..	1
Thyroid.....	2	..	..	..	..	..	1	..	1
Ureter.....	2	..	..	..	..	..	..	..	..
Broad ligament.....	1	1	..	..	..	..	..	..	..
Jugular vein.....	1	..	..	..	..	..	1	..	1
Myocardium.....	1	..	..	..	..	..	..	..	..
Rectus fascia.....	1	..	..	1	..	..	..	..	1
Seminal vesicle.....	1	..	..	..	..	..	..	..	1
Clavicular nodes.....	1	..	..	..	..	..	..	..	..
Testes.....	1	..	..	..	..	1	..	..	..
Tracheal nodes.....	1	..	..	..	..	..	..	..	..
Vagina.....	1	..	..	..	..	..	1	..	..

Secondary deposits of the growth had taken place in 240 of the 416 cases, and in the remaining 176 the lesion was entirely localized. Metastases occurred most frequently to the liver (136 cases), to the regional glands (101 cases) and to remote organs (table 7).

As was pointed out by Larson and Nordland, secondary deposits of tumor tissue occurred with the same relative frequency as the primary lesion, without regard to the location of the primary growth in the colon;

31. Mayo, W. J.: A Study of the Recto-Sigmoid, Surg., Gynec. & Obst. 25: 616 (Dec.) 1917. McArthur, L. L.: Carcinoma Rectum, *ibid.* 21:495, 1915.



hence there was no difference in the tendency to metastasize depending on the location of the primary growth in the proximal or the distal segments of the colon.

The liver was the most frequent site of metastases; it accounted for 23.1 per cent of all metastatic sites and was involved in 56.6 per cent of all cases in which metastasis occurred. Metastatic growth may appear in any part of the body, although the liver, the regional lymph nodes, the peritoneum, the pararectal nodes, the lungs and the intestine were the most frequent sites.

In lesions of the transverse colon and splenic flexure the stomach was involved by extension. This close anatomic relation not infrequently leads to difficulty in clinical determination of the site of the primary lesion.

Lesions of the rectosigmoid juncture seldom produced metastases to regional nodes (25 per cent), but remote secondary hepatic lesions were frequent (81 per cent). This, according to Gilchrist and David,<sup>32</sup> may have been due to lack of search. These authors were able to increase the number of nodes found per specimen from 23.9 to 52.1 by clearing operative specimens by a special technic of examination.

Extension into lymph nodes cannot be accurately determined by gross examination, as was shown by Gabriel, Dukes and Bussey,<sup>33</sup> who tried to determine by gross methods the presence of carcinoma in 1,242 nodes found in operative specimens of carcinoma of the rectum. Of 337 nodes considered grossly to contain carcinoma, only 132 were seen to be involved on microscopic examination; and of 905 nodes considered to be free of carcinoma, 18 contained carcinoma microscopically.

*G. Surgical Intervention.*—An analysis of the pathologic observations in 265 cases of this series in which surgical treatment was used revealed that 43 per cent of the carcinomas at the time of death were limited to involvement of the colon. In approximately 50 per cent of the autopsy series the tumors were operable according to the standards of Melchior,<sup>34</sup> who stated that operable tumors are those with which removal of the primary growth and its adjoining metastases is technically possible, eliminating those with which the immediate operative risk is too great and those for which advanced age or accompanying disease makes radical operation inadvisable.

In this group of 265 operatively treated patients, some died from causes attending operation or remote from operation, other than those

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32. Gilchrist, R. K., and David, V. C.: Lymphatic Spread of Carcinoma of Rectum, *Ann. Surg.* **108**:621 (Oct.) 1938.

33. Gabriel, W. B.; Dukes, C., and Bussey, H. J. R.: Lymphatic Spread in Cancer of Rectum, *Brit. J. Surg.* **23**:395 (Oct.) 1935.

34. Melchior, E.: Zur Beurteilung der Operabilität maligner Tumoren, *München. med. Wchnschr.* **79**:784 (May 13) 1932.

directly pertaining to the effects of cancer. For 172 patients the pathologist attributed death to some immediate surgical complication, such as surgical shock, technical surgical errors, such as operative soiling, or mechanical obstruction, and in 1 instance the surgeon inadvertently closed the proximal instead of the distal loop of intestine within the peritoneal cavity in preparation for a two stage operative procedure.

Table 8 shows the pathologic diagnosis of the cause of death of 172 patients subjected to operation. Peritonitis (40.7 per cent) and pneumonia (17.4 per cent) accounted for more than half of the deaths in this group.

TABLE 8.—*Anatomic Diagnosis of Cause of Death in One Hundred and Seventy-Two Cases of Carcinoma of the Large Intestine Subjected to Surgical Treatment*

Cause of Death	Cecum and Ascend- ing Colon	Hepatic Flexure	Trans- verse Colon	Splenic Flexure	Descend- ing Colon	Sigmoid Flexure	Rec- tosig- moid	Rectum
Coronary sclerosis.....	1	..	..	..	..	..	..	3
Evisceration.....	1	1	..	..	..	..	..	2
Gangrene of the bowel.....	1	..	..	..	..	1	..	2
Ileus.....	..	..	..	..	..	1	..	2
Isolated loop obstruction.....	..	..	..	..	..	..	..	1
Mechanical obstruction.....	3	..	..	..	..	4	4	3
Meningitis.....	..	..	..	..	1	..	..	1
Parotitis.....	..	..	1	..	1	..	..	..
Perforation peritonitis.....	1	..	..	..	..	..	..	..
Peritonitis.....	17	1	3	2	3	21	6	17
Pneumonia.....	7	..	..	..	..	11	3	9
Prolapse colostomy.....	..	..	..	..	..	..	..	1
Pulmonary atelectasis.....	2	..	..	..	..	..	..	..
Pulmonary embolism.....	..	..	1	..	1	3	1	4
Pulmonary thrombosis.....	1	..	..	..	..	1	1	..
Pyelonephritis.....	..	..	..	..	..	..	..	2
Shock.....	4	..	..	..	1	5	1	..
Thrombosis of iliac vein.....	1	..	..	..	..	..	..	2
Uremia.....	..	..	..	..	..	..	..	2
Wound infection.....	..	..	..	..	..	..	..	..
Miscellaneous.....	3	..	..	..	..	..	..	..
	42	2	5	2	6	47	16	52

#### SUMMARY

Autopsy records of 416 cases of malignant tumor of the large intestine have been reviewed. Males with carcinoma of the large intestine comprised 15.2 of every thousand males on whom autopsy was performed, while females with carcinoma of the large intestine comprised 18.2 of every thousand females on whom autopsy was performed. The average age for the group of 416 patients at the time of death was 50.5 years. The greatest incidence of cancer was in the fifth, sixth and seventh decades.

The rectum, the sigmoid flexure and the cecum were found to be the most common sites of cancer.

The average duration of symptoms was thirteen months for lesions of the right side of the colon; twelve and one-half months for lesions of the transverse and descending colon, and fourteen months for lesions of the sigmoid flexure.

Early symptoms of carcinoma of the large intestine may appear relatively insignificant to both the patient and the physician. The confusing clinical picture presented by such carcinomatous lesions resulted in 31 per cent of incorrect diagnoses. Four per cent of the growths were asymptomatic up to the onset of acute obstruction.

Of 119 rectal cancers, 48 per cent were correctly diagnosed. A higher percentage of correct diagnoses was noted for lesions in the distal portion of the colon than for lesions in the proximal portion. Sixteen per cent of the cecal lesions incorrectly diagnosed were called appendicitis.

A change of intestinal habit was experienced by 62.3 per cent of the patients. Alternating constipation and diarrhea occurred in 2.7 per cent of 371. A change in the character of the stool was infrequent in cases of cancer of the distal part of the colon.

Nausea and vomiting were late symptoms, and they occurred most often with lesions of the cecum and of the sigmoid flexure. Loss of weight occurred late in 85 per cent of the patients. Forty-three per cent of the patients had no symptoms of colonic obstruction. Complete obstruction was associated with 23.1 per cent of 121 lesions in the proximal portion of the colon and 33.2 per cent of 232 lesions in the distal portion.

Bleeding did not occur in 8.6 per cent of 123 cases, either grossly or by chemical tests. Carcinoma of the cecum and ascending colon presented the clinical picture of anemia, for which patients were treated over prolonged periods. The lowest values for hemoglobin were associated with lesions in the proximal portion of the colon.

Hemorrhoids were associated lesions in 9.4 per cent of the cases.

Pain or distress was absent in 7 per cent of 258 patients. A palpable tumor was found in 29.7 per cent of 371. Seventy-six per cent of lesions within 10 cm. of the anal ring were not diagnosed by the referring physician.

Diagnosis by biopsy in 3 of 39 cases in which biopsy was performed was not in agreement with the anatomic diagnosis. Ninety-seven diagnoses reported after roentgen studies of the colon were correct in 85 per cent of the cases examined.

Metastases were present in 57 per cent of the patients. Metastatic deposits of tumor tissue occurred with the same relative frequency as the primary lesions, without regard to the site of the primary growth. The liver was the favorite site for metastases, constituting 23.1 per cent of all sites of metastasis and being affected in 56.6 per cent of all cases in which metastasis occurred.

The carcinomas were confined to the colon at the time of death in 43 per cent of the 265 patients subjected to surgical treatment.

Peritonitis (40.7 per cent) and pneumonia (17.4 per cent) accounted for more than half the anatomic causes of death.

It is granted that the autopsy record probably should not be utilized as a source of data concerning the clinical history of disease. On the other hand, if the autopsy is to function otherwise than as a mere verification of the cause of death, some attention must necessarily be given to important clinical signs and symptoms.

Schereschewsky,<sup>35</sup> in discussing the Bone Act establishing the National Cancer Institute, outlined a nation-wide campaign to produce results in the control of cancer commensurate with its degree of perfection. The details on which such perfection depends must be delegated to persons actively engaged in some special phase of the cancer problem. The trainee in cancer, under the direction of the National Cancer Institute, should participate in the responsibility for the success of cancer control. In the cancer clinic the trainee could advantageously be given the responsibility of correlating, according to previously set up schedules of information, the clinicopathologic observations in each case of postmortem examination for cancer. Such a plan carried out over a five year period in all the cancer institutes harboring trainees would provide a fund of information of inestimable value.

#### CONCLUSIONS

1. The relation of age, sex and site in this series of malignant lesions of the large intestine apparently presents no evidence of geographic influence when compared to the experience generally encountered in other sections of the country.

2. The early symptoms of this disease are not yet sufficiently well understood by the patient or by the physician to enable one to avoid late diagnosis and treatment in the majority of cases.

3. The early clinical pattern of malignant disease of the colon presents no specific symptoms. It is not until hemorrhage or interference with function appears that the patient seeks medical advice. Therefore melena, change in intestinal habit, weakness, anemia, loss of weight or signs of colonic obstruction, whenever present and in whatever combination, should be thoroughly investigated to rule out the presence of carcinoma of the large intestine before the patient's complaint is treated symptomatically.

4. Reliable clinical proof of early colonic cancer depends on the roentgen ray. Digital examination of the rectum and the use of the sigmoidoscope are important for recognition of neoplastic lesions of the distal segments of the colon.

Dr. E. T. Bell of the department of pathology furnished the material used in this study.

New Hampton Clinic.

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35. Schereschewsky, J. W.: The Prevention and Control of Cancer: A Plan for Nation-Wide Organization, *Pub. Health Rep.* **53**:961 (June 17) 1938.

# SURGICAL LESIONS OF THE PANCREAS

A REVIEW

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In the last fifteen years knowledge of lesions of the pancreas and skill in their surgical management have advanced extraordinarily, both because the syndrome of hyperinsulinism has become widely known and because surgeons in constantly increasing numbers have carried out operative procedures on the pancreas. Surgical treatment of the pancreas consequently has assumed for the general surgeon sufficient importance to make a review of the subject distinctly worth while.

From Jan. 1, 1935 to Dec. 31, 1939, inclusive, at the Mayo Clinic, 255 operations were performed for lesions of the pancreas. This number means approximately that of every 1,500 patients registered in that period 1 patient was operated on for disease of the pancreas. When one recognizes that in the same period 4,437 operations were performed on the gallbladder for cholecystitis, acute or chronic, and 1,488 operations on the bile ducts, one gains a clearer idea of the frequency with which pancreatic lesions occur. For 1 operation on the pancreas, about 25 operations were carried out on the gallbladder and on the ducts.

One hundred and eighty-five (73 per cent) of the lesions of the pancreas for which operation was performed from 1935 to 1939 inclusive at the Mayo Clinic were considered malignant. Thus, the relative importance of malignant tumor among pancreatic lesions becomes manifest. One patient in, roughly, every 1,800 registrations at the clinic is operated on for malignant tumor of the pancreas. Hoffman<sup>1</sup> estimated that more than 4,000 deaths annually occur in the United States from carcinoma of the pancreas. Bigelow and Lombard<sup>2</sup> found that 4.8 per cent of all deaths from cancer in Massachusetts were due to carcinoma of the pancreas.

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From the Division of Surgery, the Mayo Clinic.

1. Hoffman, F. L., cited by Clute, H. M.: The Problem of Cancer of the Pancreas, *J. A. M. A.* **107**:91-97 (July 11) 1936.

2. Bigelow, G. H., and Lombard, H. L., cited by Clute, H. M.: The Problem of Cancer of the Pancreas, *J. A. M. A.* **107**:91-97 (July 11) 1936.

Seventy (27 per cent) of the 255 lesions of the pancreas operated on from 1935 to 1939 inclusive at the clinic were benign. The distribution of these lesions is seen in table 1.

#### TESTS OF PANCREATIC FUNCTION

Clinical tests of pancreatic function, although still not completely satisfactory, have made it possible to obtain fairly definite information as to the condition of the gland. The useful tests are of three types: first, tests of the blood serum for lipase and amylase; second, tests of the pancreatic juice for ferments with and without stimulation by the hormone, secretin, and, third, tests of the stools.

It should be emphasized that tests for lipase and for amylase in the blood serum are usually of value only within a week or ten days after the onset of a lesion of the pancreas. Elevations in the values for these substances are efficient indicators of disease in the pancreas, as Comfort

TABLE 1—*Operations for Lesions of the Pancreas (1935 to 1939, Inclusive)*

Malignant lesions		185
Benign lesions		70
Pancreatitis	28	
Cyst	22	
Adenoma (islet cells)	4	
Hyperinsulinism (no tumor)	3	
Accessory pancreas	9	
	2	
	1	
removal of portion in course of other operation	1	
Total		255

and his associates<sup>3</sup> have shown, although the elevations do not indicate the nature of the disease. The determination of the level of serum lipase appears to be the more reliable; in almost every instance this test if used within a week or ten days after the onset of acute pancreatitis discloses an increased value for lipase. The value for serum amylase may also be found increased under similar conditions, but it returns to normal earlier than does that for serum lipase. If perforating peptic ulcer or carcinoma of the stomach has been diagnosed, elevations in the values for amylase and lipase may be accepted as indications of pancreatic involvement. In the presence of jaundice without distention of

3 Comfort, M. W., and Osterberg, A. E. Serum Amylase and Serum Lipase in the Diagnosis of Disease of the Pancreas, *M. Clin. North America* **24**:1137-1149 (July) 1940, The Value of Determination of the Concentration of Serum Amylase and Serum Lipase in the Diagnosis of Disease of the Pancreas, *Proc. Staff Meet., Mayo Clin.* **15**:427-432 (July 3) 1940. Comfort, M. W.; Parker, R. L., and Osterberg, A. E. The Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons with Disease of the Upper Part of the Abdomen, *Am. J. Digest Dis.* **6**:249-254 (June) 1939.

the gallbladder, elevations in the values for these ferments in the blood serum are presumptive evidence of primary or secondary carcinoma of the head of the pancreas; normal values are almost always present when malignant disease is confined to the biliary tract.

Agren and Hammarsten <sup>4</sup> in 1937 isolated in crystalline form the hormone secretin, which stimulates the flow of pancreatic juice. Lagerlöf <sup>5</sup> injected secretin intravenously after passing a double tube apparatus with one limb into the stomach and one limb into the duodenum and was able to aspirate almost uncontaminated pancreatic secretion. This procedure has become the basis of the secretin test, with which a high degree of accuracy in the determination of pancreatic function is obtained. Several interesting facts have been elicited by this method: First, the volume of pancreatic secretion is in direct proportion to the amount of secretin injected; second, the amount of enzymes secreted is in inverse proportion to the volume of pancreatic juice both in health and in disease, and, third, in disease the amount of enzymes secreted is less. The first function of the pancreas to fail when the organ is diseased is the production of enzymes; of these, amylase disappears first. Thus, in the presence of acute pancreatitis there may be no amylase, while trypsin or lipase may be present in normal amount. The secretion of all ferments as well as of bicarbonates usually is reduced by pancreatic calculi and by such lesions as carcinoma of the pancreas and pancreatic necrosis. If the gallbladder is normal secretin will not cause bile to flow, but when the gallbladder is diseased or absent secretin will cause bile to flow. This action indicates whether or not the gallbladder is functioning and supports the evidence given by roentgen studies of the gallbladder.

An excess of fat in the stools is probably of pancreatic origin if the nitrogen lost in the stools exceeds 3 Gm. in twenty-four hours. The determination of nitrogen content is a valuable index of pancreatic function and is of assistance in the differential diagnosis of sprue and idiopathic steatorrhea.

If elevation in the values for diastase or amylase in the urine is noted within ten days of the onset of an acute illness, it is of value in the diagnosis of acute pancreatitis. All other tests are practically valueless.

#### ACUTE PANCREATITIS

Acute pancreatitis is a rare disease; only 17 cases were reported in a period of seven years at the Mayo Clinic. Abell,<sup>6</sup> in a series of 2,000

4. Agren and Hammarsten, cited by Lagerlöf.<sup>5</sup>

5. Lagerlöf, H.: The Secretin Test of Pancreatic Function, *Quart. J. Med.* 8:115-126 (April) 1939.

6. Abell, I.: Acute Pancreatitis, *Surg., Gynec. & Obst.* 66:348-353 (Feb., no 2A) 1938.

operations performed on the biliary tract, reported that pancreatitis was present in 30 cases. The disease afflicts women more frequently than men, but persons of any age may be affected. In the 17 cases observed at the clinic the patients were from 14 to 63 years of age.

Acute pancreatitis is usually secondary to disease of the biliary tract and is most often due to infection. However, less frequently trauma, vascular injury, perforated duodenal ulcer or infection associated with some other lesion in the body may be responsible for its development. Reflux of infected bile and mere secretion of bile into the pancreatic duct due to a stone in the ampulla, to spasm of the sphincter of Oddi or to edema of the papilla have been suggested as causes of the trouble. The bile produces necrosis of the pancreatic parenchyma, as Dragstedt and his associates<sup>7</sup> have shown, by the local cytolytic and destructive properties of bile salts rather than by activation of the pancreatic ferments, namely, the change of trypsinogen into trypsin, which itself was found incapable of digesting living tissue. In any event, no matter what the cause of the necrosis, severe toxemia develops from it.

Abell has divided acute pancreatitis into four types: (1) acute pancreatic edema; (2) acute pancreatic necrosis; (3) acute hemorrhagic pancreatitis, and (4) pancreatic abscess. These processes often intermingle, so that in many cases varying degrees of edema, hemorrhagic necrosis, fat necrosis and autolysis can be observed.

The diagnosis of acute pancreatitis is most difficult, and the condition rarely is diagnosed preoperatively. Severe epigastric pain extending posteriorly is the most common symptom, although at the onset the discomfort may be a dull ache which develops rapidly into acute distress. Nausea and vomiting are common. The temperature and the pulse rate are elevated; there is abdominal tenderness, usually without rigidity, and jaundice may be present. The patient looks extremely ill and often is pale, cold and clammy. In more than half the cases a history of disease of the gallbladder is elicited.

In cases of acute pancreatitis leukocytosis is present, the count averaging about 20,000 per cubic millimeter of blood during the attack. The values for diastase in the blood and in the urine usually are elevated after six or eight hours and remain so from seven to ten days, owing to liberation of ferments in the pancreatic parenchyma (the Wohlge-muth<sup>8</sup> test). The most valuable test, however, as Comfort<sup>9</sup> has shown,

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7. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Pathogenesis of Acute Pancreatitis (Acute Pancreatic Necrosis), *Arch. Surg.* **28**:232-291 (Feb.) 1934.

8. Wohlge-muth, J.: Ueber eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments, *Biochem. Ztschr.* **9**:1-9, 1908.

9. Comfort, M. W.: Serum Lipase: Its Diagnostic Value, *Am. J. Digest. Dis. & Nutrition* **3**:817-821 (Jan.) 1937.



is that for serum lipase; in 95 per cent of a series of cases of acute pancreatitis the value for lipase in the serum increased immediately after onset and over a period of three weeks gradually decreased to normal. The secretin test also detects reduction in the enzyme ferments of the pancreatic secretion. Roentgenograms of the gallbladder, stomach and kidneys may be valuable but seldom are available, as usually the patient is too ill to be subjected to elaborate tests.

In differential diagnosis, if absence of rigidity allows acute cholecystitis and perforated peptic ulcer to be ruled out; if acute mesenteric thrombosis can be excluded; if intestinal obstruction, acute appendicitis, renal stone and twisted ovarian cyst are eliminated, and if acute pancreatitis is recognized, what treatment should be instituted? Most physicians believe that immediate surgical intervention is unwise and that, assuming that a correct diagnosis can be made with reasonable certainty, operative attempts to remedy the disease in the biliary tract should be delayed from three to four weeks. Others believe that immediate operation is the best treatment and advocate a minimal procedure, such as cholecystostomy or choledochostomy with drainage. The operative mortality is high (48 per cent in 19 cases of de Klimkó<sup>10</sup>). Infrequently diabetes or a pancreatic fistula may follow acute pancreatitis.

#### CHRONIC PANCREATITIS

The diagnosis of chronic pancreatitis is a source of debate. Chronic pancreatitis, although it rarely is diagnosed preoperatively, is common in association with disease of the biliary tract. In a period of seven years at the Mayo Clinic the diagnosis was made in 1,216 cases, in the majority of which some concomitant disease of the gallbladder or of the bile ducts was present. Chronic pancreatitis usually is discovered by the surgeon in the course of an operative procedure on the gallbladder or ducts. The diagnosis, based on firmness of the pancreas to palpation by the surgeon, frequently is not confirmed at necropsy.

Treatment of the primary cause of the pancreatitis is indicated, and this usually calls for drainage of the gallbladder or of the bile ducts. As a rule, prolonged drainage of the common bile duct through a T tube, with periodic cholangiographic examinations to determine progress, is advisable, although with increasing frequency internal short-circuiting is being accomplished in cases of the more severe pancreatitis by the performance of choledochoduodenostomy.

Severe pancreatitis may be either acute or chronic. Surgical procedures carried out at the clinic for the disease in the period 1935 to 1939 inclusive are given in table 2.

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10. de Klimkó, D.: The Surgical Treatment of Acute Pancreatitis, *Surg., Gynec. & Obst.* **63**:89-95 (July) 1936.

## PANCREATIC CYST

In the period from 1935 to 1939 inclusive, 22 patients with pancreatic cyst were operated on at the clinic. From 1908 through 1939, according to a recent study by Thigpen,<sup>11</sup> 139 patients with pancreatic cyst were treated surgically at the clinic. This number represents 1 patient with cyst in approximately every 8,000 patients registered. Obviously, pancreatic cyst is a relatively rare lesion; it is most commonly encountered in women and in patients of middle age, although a person of any age may be affected.

A pancreatic cyst manifests itself usually in two ways, by tumor and by pain. The tumor ordinarily is smooth, tense and circumscribed, presenting to the left of the midline in the upper part of the abdomen, in the midline or, rarely, to the right of the midline or below the umbilicus. It may be evident between the stomach and the colon in the lesser peritoneal cavity, between the stomach and the liver or behind the colon in the layers of the mesocolon. Ordinarily it is mobile only

TABLE 2.—*Surgical Procedures Employed at Mayo Clinic for Severe Pancreatitis (1935 to 1939 Inclusive)*

Choledochostomy.....	17
Cholecystostomy.....	9
Excision of specimen.....	4
Exploration.....	1
Total procedures on 28 patients *	31

\* Three patients underwent two procedures each.

when limited to the tail of the pancreas. More than 85 per cent of patients with pancreatic cyst have pain, either dull and steady or severe and colicky, in the epigastrium or the left upper abdominal quadrant, extending to the back. Nausea, vomiting, weakness, loss of weight and even jaundice may occur. Surgical exploration may be necessary to distinguish pancreatic cyst from such other abdominal swellings as mesenteric, omental, splenic and hepatic cysts, hydrops of the gall-bladder, retroperitoneal neoplasms, hydronephrosis and aneurysms.

As a result of a review of the literature, Thigpen suggested the following etiologic classification of cysts of the pancreas: (1) pseudocyst, or a cyst without an epithelial lining, which may be the result of trauma or inflammation; (2) retention cyst, that is, a cyst resulting from obstruction to the outflow of secretion by calculi or pancreatitis; (3) neoplastic cyst, which may occur in a cystadenoma, a cystadenocarcinoma, a sarcoma or a teratoma; (4) cyst resulting from defective development, and (5) parasitic cyst, such as the hydatid variety.

11. Thigpen, F. M.: A Pathologic Study of Cysts of the Pancreas, Thesis. University of Minnesota Graduate School, 1940.

In addition, on the basis of a thorough study of 55 (all in which adequate tissue was available for study) of the 139 cases of pancreatic cyst in which operation was performed at the Mayo Clinic from 1908 to 1939 inclusive, he suggested classification on the basis of the pathologic condition present, which is given in table 3.

The first type named in table 3 is the one represented by most of the pseudocystic tumors without epithelial lining. Thigpen found that such a lesion is usually unilocular, that the diameter varies from 5 to 35 cm., and that frequently the cyst is secondary to trauma or to pancreatitis. The retention cyst, commonly associated with chronic pancreatitis or with infection in the pancreas, usually is composed of low cuboidal or epithelial cells of duct tissue, and ducts are often present. This cyst, like the type first named in table 3, occurs most commonly in the head or in the body of the pancreas. The cystadenoma is papillary, is usually

TABLE 3—*Pathologic Classification of Pancreatic Cysts: 55 Cases*

Class	Cases
Cyst with wall of fibrous connective tissue	24
Retention cyst, low cuboidal or columnar epithelium of ducts	10
Cystadenoma	7
Cystadenocarcinoma	4
Miscellaneous	7
Cystic hemangioendothelioma (malignancy, grade 2 or 4)	2
Cystic adenocarcinoma of islets of Langerhans (malignancy, grade 4)	1
Cavernous hemangioma	1
Dermoid cyst	1
Cyst of accessory pancreas	1
Sebaceous cyst lined with squamous cell epithelium	1

in the tail, is always multilocular and is not associated with a history of trauma or of biliary disease. The four cystadenocarcinomas reported on by Thigpen all showed malignancy of grade 1 or 2 (Broder's index); 1 had metastasized.

The treatment of pancreatic cyst must depend somewhat on the type of lesion. When the lesion can be completely removed, excision is advisable. Complete removal was made in 15 of the 55 cases studied in detail by Thigpen. Partial removal of the cyst and drainage were carried out in 17; provision for drainage alone was made in 11, and marsupialization with drainage was performed in 12. In most instances drainage, removal or partial removal with drainage or marsupialization with drainage produces excellent results. Some authors have advocated direct anastomosis of the cyst to the stomach, to the intestine or to the gallbladder (Meyer and Rosi<sup>12</sup>) to secure internal drainage and to avoid prolonged external drainage, this operation has not been used at the Mayo Clinic.

<sup>12</sup> Meyer, K. A., and Rosi, P. A. Internal Drainage of Pancreatic Cyst. *Proc Inst Med Chicago* 11:59 (March 15) 1936

In some instances cholecystogastrostomy or choledochoduodenostomy should be performed to relieve obstructive jaundice due to pressure of the cyst on the common duct. In at least 1 such case, in which a calcified cyst could not be removed from the head of the pancreas, this procedure was employed.

#### PANCREATIC LITHIASIS

Pancreatic calculi were first noted by de Graaf<sup>13</sup> in 1667. Capparelli<sup>14</sup> in 1883 performed the first operative removal of calculi from the pancreas. Haggard and Kirtley,<sup>15</sup> in 1938, reviewed 65 operative cases and 139 nonoperative cases of pancreatic lithiasis (1667 to 1938). In 29 cases of the latter group the calculi were revealed by roentgen examination and in 110 they were discovered at necropsy. Haggard and Kirtley concluded that, as 102 of the 204 cases were observed between 1925 and 1938, the condition is not so rare as has been generally supposed. J. G. Mayo<sup>16</sup> reviewed the subject in 1936 and reported a total of 25 cases observed at the Mayo Clinic.

The cause of pancreatic lithiasis is not known. There are two types of calculi, true pancreatic stones, found in the ducts, and false stones, which seem to be calcifications in the parenchyma probably resulting from pancreatitis secondary to disease of the biliary tract. Stones in the ducts may result from infection, with perhaps stasis and changes in secretion. The stones usually consist of calcium carbonate, a constituent not found in normal pancreatic secretion, or of salts of magnesium or phosphorus, together with organic matter. The stones may vary in number from one to three hundred and in size from that of a small pea to that of a walnut, and they are usually whitish gray. In most cases of pancreatic calculi the patients are between 35 and 50 years of age; in the series reviewed by Haggard and Kirtley there were 33 men and 28 women; the sex of 4 patients of Haggard and Kirtley's series was not given.

In all operative cases Haggard and Kirtley found that the only constant symptom was pain in the epigastric region and the left upper abdominal quadrant, often extending to the back, usually severe and colicky and frequently similar to biliary colic. Vomiting was present in 75 per cent of cases, and loss of weight and emaciation were frequent. Jaundice was present in about 30 per cent of cases, usually tended to

13. de Graaf, R., cited by Haggard and Kirtley.<sup>15</sup>

14. Capparelli, cited by Haggard and Kirtley.<sup>15</sup>

15. Haggard, W. D., and Kirtley, J. A.: Pancreatic Calculi: A Review of Sixty-Five Operative and One Hundred and Thirty-Nine Nonoperative Cases, *Tr. South. S. A.* **51**:169-184, 1938.

16. Mayo, J. G.: Pancreatic Calculi, *Proc. Staff Meet., Mayo Clin.* **11**:456-457 (July 15) 1936.

recur with each attack and was often mild and transient. Glycosuria was reported in only 6 of the 65 cases (9.2 per cent). Occasionally steatorrhea may be present, and if so the pancreas should always be investigated for calculi.

The treatment should be surgical removal of the stones, except when the calcifications are in the parenchyma of the gland, from which removal is impossible. The operative approach may be transduodenal (for removal of stones in the duct near the ampulla of Vater), or approach may be made through the gastrocolic or the gastrohepatic omentum and the gland incised directly over the stones. When the stones have been removed, the duct is closed with a silk suture. Any resulting pancreatic fistulas usually close spontaneously in a few weeks or months. Haggard and Kirtley, from their review of the literature back to the year 1667, reported a 17.2 per cent mortality for all cases; in the series of cases at the Mayo Clinic all patients operated on recovered.

When pancreatic lithiasis has existed for a prolonged period there is likely to develop not only atrophy of the pancreatic acini and fibrosis of the gland with resultant fatty infiltration of the liver, such as follow experimental pancreatectomy, but diabetes resulting from continued atrophy of the gland and infection. That fatty infiltration is commonly present in the terminal stages of diabetes as well has been proved. Dragstedt<sup>17</sup> demonstrated that a pancreatic extract controls this disposition of fat, and several cases have been reported by Snell and Comfort<sup>18</sup> and by Rosenberg<sup>19</sup> in which by the administration of a pancreatic extract, lipocaic, the fatty deposit has been made to disappear from the liver cells. J. G. Mayo reported that in 3 of 9 nonoperative cases of pancreatic lithiasis there was found at necropsy sufficient atrophy of the pancreas to produce fatty changes in the liver; thus it is important to remove calculi.

#### INJURY AND FISTULA

The pancreas, protected by the ribs above and the backbone posteriorly, rarely is injured except by extra-abdominal force, usually a stab wound or a gunshot injury. Frequently other organs are damaged as well. If the patient is able to undergo operation, suture of the pancreas and drainage of the region are necessary, as the damage to the pancreas usually is severe and the resulting shock or hemorrhage is great. The injury seldom can be diagnosed preoperatively.

17. Dragstedt, I. R., cited by Walters, W., in discussion on Haggard and Kirtley.<sup>15</sup>

18. Snell, A. M., and Comfort, M. W.: Hepatic Lesions Presumably Secondary to Pancreatic Lithiasis and Atrophy: Report of Two Cases, *Am. J. Digest. Dis. & Nutrition* 4:215-218 (June) 1937.

19. Rosenberg, D. H.: A Proved Case of Recovery from Fatty Metamorphosis of the Liver After Treatment with Lipocaic, *Am. J. Digest. Dis.* 5:607-613 (Nov.) 1938.

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A pancreatic fistula rarely develops spontaneously, although one occasionally follows traumatic rupture of the pancreas. Most frequently a fistula is encountered after an operative procedure on the pancreas, usually after operation for hyperfunctioning adenomas and pancreatic cyst, and usually it closes spontaneously within weeks or months. Successful transplantation of fistulous tracts has been performed by Lahey and Lium<sup>20</sup>; they reported also 26 cases collected from the literature in which a fistulous tract was transplanted to the stomach or to the intestine.

#### HYPERINSULINISM

Soon after Banting and Best<sup>21</sup> isolated insulin (1922), Harris<sup>22</sup> postulated a clinical syndrome which he termed hyperinsulinism. It corresponded to that resulting from overdosage with insulin, and he demonstrated cases in which the syndrome was associated with a hypoglycemic state. Since Wilder and his associates,<sup>23</sup> in 1927, reported the first authentic case of hyperinsulinism associated with tumor (carcinoma) of the islands of Langerhans, there has been more widespread interest in the syndrome, so that many cases have been reported and knowledge of the subject has increased vastly. At the Mayo Clinic to October 1940 there had been 45 cases in which there was sufficient evidence to justify suspicion of the presence of a hyperfunctioning adenoma of the islands of Langerhans. In 16 of these cases a tumor of the islands of Langerhans was discovered at surgical operation; in 18, exploratory operation did not reveal tumor; 11 patients, in spite of sufficient evidence to justify the diagnosis, for one reason or another refused operation.

The symptoms of hyperinsulinism are protean. They range from minor nervous and digestive disturbances, such as restlessness, hunger, fatigue, confusion, pseudodrunken behavior, irritability, diplopia and aphasia, to major nervous and digestive troubles, such as convulsive seizures, delirium, mania, stupor, unconsciousness and coma. The attacks are associated frequently with unusual exercise or fasting and typically are relieved by ingestion of dextrose and food. Invariably,

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20. Lahey, F. H., and Lium, R.: Cure of Pancreatic Fistula by Pancreato-jejunostomy: Report of Case with Review of Literature, *Surg., Gynec. & Obst.* **64**:79-88 (Jan.) 1937.

21. Banting, F. G., and Best, C. H.: The Internal Secretion of the Pancreas, *J. Lab. & Clin. Med.* **7**:251-266 (Feb.) 1922; Pancreatic Extracts, *ibid.* **7**:464-472 (May) 1922.

22. Harris, S., cited by Whipple, A. O., and Frantz, V. K.: Adenoma of Islet Cells with Hyperinsulinism: A Review, *Ann. Surg.* **101**:1299-1335 (June) 1935.

23. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas: Hyperinsulinism and Hypoglycemia, *J. A. M. A.* **89**:348-355 (July 30) 1927.



before any patient is subjected to surgical exploration of the pancreas, the Whipple triad<sup>24</sup> of (1) nervous and digestive disorders, (2) a concentration of blood sugar of 50 mg. per hundred cubic centimeters or less and (3) typical relief from ingestion or injection of dextrose should be present. Roentgen examination of the sella turcica should be made to exclude pituitary disorder and tumor of the brain, and every effort should be made to rule out other common causes of the hypoglycemic state, including possible pathologic conditions of the thyroid gland, the adrenal glands and the liver.

Once a patient has been found to have hyperinsulinism by the criterion known as the Whipple triad, surgical exploration of the pancreas definitely is indicated, for in approximately two thirds of the cases tumor of the islands of Langerhans will be present. Whipple,<sup>25</sup> in his latest review of the condition (December 1939), reported 82 cases in which tumor was found on surgical operation and 47 in which exploratory operation did not reveal tumor. However, of the 47 cases in which surgical exploration was made a tumor was found at necropsy in 4, at secondary operation in 6 and in a resected portion of pancreas in 4. In another study, of 14 cases of tumor of the islands of Langerhans at first overlooked (in 9 cases discovered at reoperation and in 5 at necropsy), Whipple found that in 7 cases the growth was located in the head, in 5 in the tail and in 2 in the body of the pancreas. Also, 4 of Whipple's patients underwent partial resection of the pancreas without relief of hypoglycemia, and at subsequent operation an adenoma was found in the head of the pancreas.

The foregoing comment brings to mind two of the chief difficulties encountered in a consideration of surgical treatment of the pancreas for hyperinsulinism, namely, the location of a tumor when present and the treatment indicated when a tumor is not found. In order properly to explore for tumor it is of prime importance to obtain adequate exposure of the pancreas. As in some cases the growth may be only 0.5 cm. in diameter or even smaller, the problem is difficult, as is evidenced by the number of instances in which a tumor has been missed at the first operation and found subsequently.

The initial surgical approach is best made through the gastrocolic omentum, the stomach being elevated with retractors and the colon displaced downward. This preparation gives excellent exposure of the body and tail. The pancreas is freed from its posterior attachment by gentle finger dissection, and the gland is palpated between the index and middle fingers posteriorly and with the thumb anteriorly. In this fashion the entire body and tail not only can be inspected but can be

24. Whipple, A. O.: The Surgical Therapy of Hyperinsulinism, *J. internat. de chir.* 3:237-276, 1938.

25. Whipple, A. O., cited by David.<sup>26</sup>

palpated for variations in consistency which may be indicative of a tumor in the middle of the gland. There is always perceptible a rather definite change in texture when one slides the fingers over the adenoma; usually a clearly circumscribed region of induration is felt. In order properly to examine and palpate the head of the pancreas it may be necessary to mobilize (kocherize) the duodenum by freeing it from its peritoneal attachment. The duodenum then is reflected downward and medialward, displaying the entire head. This procedure was used most effectively in one of our most recent cases; an adenoma of the pancreas which was revealed by palpation between the fingers was removed successfully from the region of the ampulla of Vater. One should never consider the operation complete until the entire pancreas has been thoroughly examined. In our experience the tumor rarely shells out easily; it is best excised in a wedge of pancreatic tissue. The opening in the pancreas is then sutured with silk ligatures, and the gastrocolic omentum and the abdomen are closed, with drainage to the site of excision of the tumor. A pancreatic fistula not infrequently follows this procedure, but spontaneous closure occurs usually in from a few weeks to a few months. Temporary diabetes may follow the removal of a hyperfunctioning tumor, much as tetany occurs temporarily after removal of a parathyroid tumor or evidence of insufficiency of the adrenal cortex after excision of a hyperfunctioning tumor of this structure, but it usually clears spontaneously in a few days.

When careful inspection and palpation as described fail to reveal a tumor in the pancreas, it is debatable what procedure offers most help to the patient. David,<sup>26</sup> in reporting his recent study of the results of pancreatectomy, stated that subtotal resection has given fairly satisfactory results. In 23 cases of hyperinsulinism in which subtotal pancreatectomy (90 per cent of the gland, i. e., 35 Gm. or more) was performed, a tumor was found in the resected tissue in 2 cases. Thus, of 21 patients without tumor, 14 were cured by this procedure, and the condition of 2 was improved; 4 were not benefited, and 1 died. In other words, subtotal pancreatectomy cured 66 per cent of the patients who did not have a tumor and benefited 9 per cent more. David stated that after partial, not subtotal, resection of the pancreas in the absence of tumor in 18 cases only 3 patients were cured and the condition of 3 was improved (33 per cent cured or improved). The mortality rate for subtotal resection was 4.3 per cent. Hence he concluded that subtotal (90 per cent) resection of the pancreas offers the best chance of cure when tumor is not demonstrable. We have seen almost total resection (merely a fringe of pancreas remaining at the ampulla of Vater) fail to relieve hypoglycemic crises in 1 case.

26. David, V. C.: The Indications and Results of Pancreatectomy for Hypoglycemia, *Surgery* 8:212-224 (Aug.) 1940.

Ligation of the entire thickness of the pancreas with silk sutures at the junction of the body and head just to the left of the origin of the superior mesenteric artery has been performed 4 times by us in cases in which there was no tumor. Although some amelioration of symptoms was noted in all cases, in none was the procedure curative. Pancreatic fistula followed this procedure in 2 of the 4 cases.

The question of the malignancy of these tumors of the islands of Langerhans has been debated extensively. Frantz,<sup>27</sup> in a recent review of all of Whipple's collected cases in which pathologic data were available, found that to December 1939, 46 tumors removed at operation and 24 tumors found at necropsy were considered benign and that 19 tumors removed at operation and 2 identified at necropsy were suspected of being malignant. There were 5 islet tumors with metastasis which were proved malignant. Thus, of 96 tumors, 70 were definitely benign and 26 were malignant or questionably so. Whipple<sup>25</sup> in the 82 surgical cases which he reviewed classified 65 lesions as adenomas, 2 as atypical tumors and 15 as carcinomas. Therefore, early diagnosis and removal are imperative if the patients are to receive benefit.

The results following removal of islet cell tumors are excellent. Whipple<sup>25</sup> showed that 62 of 69 patients who survived surgical intervention were cured. The operative mortality rate for the series of 82 cases was 16 per cent (13 patients).

Of the 16 cases in which a presumably hyperfunctioning tumor of the islands of Langerhans was found at surgical exploration at the Mayo Clinic, removal was undertaken in 12. In the 4 cases of inoperable carcinoma biopsy of metastatic lesions in the liver was made three times, and in 1 case, in which there was a large tumor in the midportion of the pancreas with moderate fixation and invasion of blood vessels, biopsy was performed once. All but 1 of the 4 patients who were not subjected to removal of the cancer died from three weeks to six months after removal of the biopsy specimen. The surviving patient underwent successful removal of the carcinoma elsewhere and apparently was well a year after the operation. Among the 12 patients who were operated on for removal of hyperfunctioning islet cell tumor there were 3 postoperative deaths, 2 from pneumonia (the patients were very obese) and 1 from sepsis. In 2 of the 3 cases the tumor was an adenocarcinoma, and in 1 a benign adenoma was present. Of the 9 patients who survived removal of the tumor, 2 had an adenocarcinomatous lesion and 7 a benign lesion. In 4 of these 9 survivors a pancreatic fistula developed; in each the fistula closed spontaneously in a few weeks to a few months. One patient had severe internal hemorrhage associated with a slough of a

27. Frantz, V. K.: Tumors of Islet Cells with Hyperinsulinism: Benign, Malignant and Questionable, *Ann. Surg.* **112**:161-176 (Aug.) 1940.

portion of the pancreas. One patient had an extensive pulmonary embolism, from which she recovered under treatment with heparin and oxygen. All of the 9 survivors were well when last heard from.

#### ACCESSORY PANCREAS

Although an accessory pancreas rarely produces symptoms from which relief is sought by the patient and is considered as more or less a pathologic curiosity usually seen at necropsy, the surgeon should be acquainted with this condition. There have been recorded in the literature, according to a recent study by Derbyshire,<sup>28</sup> approximately 222 cases of accessory pancreas, in 90 per cent of which the anomalous organ was in the stomach, duodenum or jejunum, in the greatest number in the duodenum; in 6 per cent it was in the ileum, and in 2 per cent, in Meckel's diverticulum. At the Mayo Clinic from 1915 to 1938 inclusive, 112 cases of accessory pancreas were recorded in the files of the department of pathologic anatomy, an incidence of 1.5 per cent in 7,504 necropsies; since 1935, 10 cases have been reported from the division of surgery.

Patients with this pancreatic disease for which surgical operation is advised usually have symptoms of two types; either they have a vague form of dyspepsia with intolerance of food and discomfort somewhat atypical of disease of the gallbladder or peptic ulcer, or they suffer from an acute abdominal condition, such as an intussusception, with nausea, vomiting and so forth, which constitutes a surgical emergency. In our series of cases at the clinic there were 2 patients with vague symptoms of dyspepsia (distress in the epigastric region and in the right upper abdominal quadrant which was aggravated by taking fatty and fried foods); roentgen examination of the stomach of 1 of these patients revealed a gastric polyp, and examination of the other patient, a circumscribed tumor, probably benign, on the posterior gastric wall, near the lesser curvature. In these 2 patients the polyp and the tumor were accessory pancreatic tissue in the gastric wall. A third surgical patient, a baby, was brought to the clinic because he had had sudden pain and nausea and had passed blood by rectum. A tumor could be palpated in the right portion of the abdomen. The obvious diagnosis was intussusception; exploratory operation revealed invagination of 12 inches (30 cm.) of gangrenous bowel; an accessory pancreas in the ileum formed a tumor at the head of the intussusception. In 2 cases of vague dyspepsia, 1 patient had an accessory pancreas in the wall of the duodenum, and the other, an accessory pancreas in Meckel's diverticulum of the ileum. In another case the anomalous pancreas was causing

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28. Derbyshire, R. C.: *Studies of Accessory Pancreas*, Thesis, University of Minnesota Graduate School, 1940.

obstruction of the stomach, for which partial gastrectomy was performed. In each of 4 cases an accessory pancreas was found incidentally at surgical operation and was removed: in 1 case, from the duodenum in the course of a gastric resection for duodenal ulcer; in 1, from the duodenum in the course of gastric resection for gastric ulcer; in 1, from the jejunum in the course of an operation for duodenal ulcer, and in 1, from the gastrohepatic omentum in the course of a gastric resection for carcinoma of the stomach.

The treatment of an accessory pancreas which is causing symptoms is excision.

#### MALIGNANT TUMOR OF THE PANCREAS

A malignant tumor of the pancreas usually arises from the alveolar pouches or ducts and is adenocarcinomatous. It may arise from the islands of Langerhans. Rarely it is sarcoma arising from the parenchyma. The growth spreads by direct extension and metastasizes through the lymph circulation and the blood stream. The lymph nodes and the liver are involved early, as is evidenced by the fact that in 50 per cent of cases in which exploratory operation was performed at the clinic metastatic lesions were found. A malignant pancreatic growth not only may impinge on the common duct and produce jaundice (Eusterman and Wilbur<sup>29</sup> reported that 78 per cent of 312 patients with a malignant lesion of the pancreas seen at the clinic from 1921 to 1931 had jaundice) but may obstruct the pylorus or the duodenum. Seventeen per cent of 113 patients on whom cholecystenterostomy was performed at the clinic for a malignant growth of the pancreas had associated duodenal obstruction.

The site of the lesion is most commonly the head of the pancreas. Leven,<sup>30</sup> reporting a series of 687 cases of carcinoma of the pancreas, stated that in 56.3 per cent the lesion was in the head and that in 30.7 per cent the carcinoma was diffuse, involving the head; in 6.6 per cent the lesion was confined to the tail, and in 6.4 per cent it was confined to the body. Since in more than three fourths of the cases the head is involved, the relative frequency of associated jaundice can be readily understood, and it can be seen why cancer of the pancreas is the third most common cause of jaundice.

The incidence of carcinoma of the pancreas is from three to four times greater among men than among women. Most of the patients are between 40 and 70 years of age; in the series reported by Eusterman and Wilbur, 72 per cent of patients were within this age group.

29. Eusterman, G. B., and Wilbur, D. L.: Primary Malignant Neoplasm of Pancreas: A Clinical Study of Eighty-Eight Verified Cases Without Jaundice, *South. M. J.* **26**:875-883 (Oct.) 1933.

30. Leven, N. L., cited by Clute, H. M.: The Problem of Cancer of the Pancreas, *J. A. M. A.* **107**:91-97 (July 11) 1936.

Most commonly rapid loss of weight and progressive painless jaundice bring the patient to the physician. There may be dull epigastric pain which extends posteriorly; it is unrelated to the food cycle and is often worse at night. Digestive distress with flatus and a feeling of fulness may be present. Latter and Wilbur<sup>31</sup> have called attention to the neurologic and psychic manifestations of carcinoma of the pancreas.

Although it may be difficult to palpate a carcinoma of the pancreas without anesthesia, examination may reveal a palpable mass (according to Rives and his associates,<sup>32</sup> this was observed in 60 per cent of a series of 96 cases). Absence of bile on repeated duodenal drainage is often encountered when jaundice is present, as it was in 78 per cent of cases in the clinic series. Roentgen examination may reveal a lesion in the vicinity of the pancreas by giving evidence of obstruction of the duodenum by an extrinsic mass, by disclosing a filling defect in the stomach caused by pressure of an extragastric mass or by expansion of the shadow of the horseshoe curve of the duodenum. Gastroscopic examination may be helpful in localization of the lesion when jaundice is not present, as was suggested by Moersch and Comfort<sup>33</sup> in discussion of 2 cases which they reported.

The differential diagnosis of factors producing obstructive jaundice is difficult. Through years of observation a syndrome of biliary colic, chills, fever and jaundice has become associated in the surgeon's mind with obstruction of the common bile duct due to stones, whereas painless progressive jaundice with a palpable gallbladder is associated with tumor in the head of the pancreas or in the ampulla of Vater. These conditions, while correct in the majority of instances, should not be taken as inflexible criteria, for occasionally all signs fail, and because of a too ready diagnosis a patient may be deprived unnecessarily of the benefits of surgical measures. For example, of 219 consecutive cases of obstructive jaundice due to stones in the common duct at the Mayo Clinic, reported by Trueman<sup>34</sup> and one of us (Walters<sup>35</sup>), in 50, or 22.8 per cent, the onset of jaundice was painless. Similarly, incomplete obstruction due to tumor may give the classic picture of stone in the common bile duct. Hence, in every case of obstructive jaundice exploratory operation should be performed if the patient's condition permits.

31. Latter, K. A., and Wilbur, D. L.: *Psychic and Neurologic Manifestations of Carcinoma of Pancreas*, Proc. Staff Meet., Mayo Clin. **12**:457-462 (July 21) 1937.

32. Rives, J. D.; Romano, S. A., and Sandifer, F. M., Jr.: *Carcinoma of Pancreas, Surg., Gynec. & Obst.* **65**:164-177 (Aug.) 1937.

33. Moersch, H. J., and Comfort, M. W.: *Gastroscopy as an Aid in the Diagnosis of Carcinoma of the Pancreas*, Am. J. Surg. **46**:246-249 (Nov.) 1939.

34. Trueman, K. R.: *Symptoms of Common Duct Stone: Review of Two Hundred and Nineteen Cases*, Proc. Staff Meet., Mayo Clin. **15**:283-284 (May 1) 1940.

35. Walters, W., in discussion on Trueman.<sup>34</sup>

Theoretically the treatment of carcinoma of the pancreas should be radical removal of the lesion, as for other forms of cancer, when conditions permit. The difficulties of radical operation are extremely great, however, for, owing to jaundice, to cachexia and to early metastasis of the disease which often is not apparent, the patient is usually in poor condition to stand such drastic treatment. The results obtained by using the procedure of Whipple have not been so satisfactory as was hoped.

Whipple<sup>36</sup> and Parsons<sup>37</sup> have performed 6 resections of the pancreas for carcinoma. The first of these, a one stage procedure, resulted in an operative death, which influenced them to adopt the more conservative two stage method, which Brunschwig<sup>38</sup> already had successfully employed. They have utilized this method 5 times, with 1 operative death from septicemia. Of the 4 patients who survived the operation, 1 was well nine months later; 2 died nine months after operation, and 1 died twenty-seven months after operation.

In the first stage of the procedure they perform gastroenterostomy, cholecystojejunostomy or cholecystogastrostomy and ligate the common bile duct. The second stage of the operation, which is performed three to four weeks later, consists of the following steps:

(a) Ligation of the pancreaticoduodenal and gastroduodenal arteries.<sup>39</sup>

(b) Resection of the descending portion of the duodenum with inversion of the upper and lower ends, and a V-shaped excision of the head of the pancreas wide of the growth together with the common duct, using the silk ligatures as a guide to the lower cut end of the duct.

(c) A ligation of the cut end of the duct of Wirsung—and the duct of Santorini, if present—and the suturing of the two cut surfaces with interrupted fine silk.

Approximately 15 per cent of all pancreatic lesions suspected of being carcinoma, as Dehne and one of us (Walters)<sup>40</sup> have shown in follow-up studies, are not malignant but inflammatory and can be cured by short-circuiting operations. Hartman,<sup>41</sup> in postmortem studies, has shown that 5 of 26 tumors of the pancreas producing jaundice were not malignant lesions but inflammatory masses.

By and large, when jaundice is present, even though metastasis has occurred, the best treatment is short-circuiting the bile back into the

36. Whipple, A. O.: Surgical Treatment of Carcinoma of the Ampullary Region and Head of the Pancreas, *Am. J. Surg.* **40**:260-263 (April) 1938; footnote 24.

37. Parsons, W. B.: Personal communication to the authors.

38. Brunschwig, A.: Resection of Head of Pancreas and Duodenum for Carcinoma—Pancreatoduodenectomy, *Surg., Gynec. & Obst.* **65**:681-684 (Nov.) 1937.

39. Whipple, A. O.; Parsons, W. B., and Mullins, C. R.: Treatment of Carcinoma of the Ampulla of Vater, *Ann. Surg.* **102**:763-779 (Oct.) 1935.

40. Walters, W., and Dehne, E. A.: Jaundice Caused by Pancreatic Lesions, *Surg., Gynec. & Obst.* **54**:832-835 (May) 1932.

41. Hartman, H. R.: Jaundice in Surgical Cholecystitis Without Stones, *M. Clin. North America* **7**:89-95 (July) 1923.

gastrointestinal tract. Moynihan<sup>42</sup> said that the risk of operation in these cases is lower than that of suicide, to which patients are goaded by the intense itching which accompanies the jaundice. Judd and Hoerner<sup>43</sup> reported relief of jaundice by short-circuiting operations in all but 4 per cent of 179 cases of jaundice due to carcinoma of the head of the pancreas or of the ampulla of Vater. The risk of operating on a jaundiced patient is justified not only because itching can be relieved but because in 22.8 per cent of cases stones in the common duct produce a syndrome which cannot be distinguished from that of carcinoma of the pancreas; in from 15 to 20 per cent of the cases the tumor is inflammatory, and in these cases operation offers cure. The relief of jaundice usually allows a patient with carcinoma of the pancreas to live comfortably to the end (table 4).

TABLE 4.—*Operative Procedures on 185 Patients with Carcinoma of the Pancreas (1935 to 1939 Inclusive)*

Procedure	Number
Cholecystogastrostomy.....	94
Cholecystostomy and choledochostomy (one or both).....	10
Cholecystoduodenostomy.....	7
Choledochoduodenostomy.....	7
Cholecystojejunostomy.....	2
Resection.....	1
Dilation of cholecystogastrostomy opening.....	1
Gastroenterostomy *.....	17
Exploration.....	53
Patient jaundiced; condition inoperable because of cirrhosis, involvement of hepatic ducts, etc.....	6
Carcinoma of islands of Langerhans.....	2
No jaundice; no obstruction.....	22
No jaundice; no obstruction; hepatic metastasis.....	20
No jaundice; no obstruction; no ascites.....	3
Total .....	192

\* Seven patients also underwent another procedure.

As a rule, the form of short-circuiting operation which is easiest in the individual case is the best. Anastomosis of the gallbladder and the stomach infrequently is followed by cholangitis, according to our experience and that of Wangensteen,<sup>44</sup> and usually patients are little disturbed by the presence of bile in the stomach. A one stage procedure usually is employed at the clinic.

42. Moynihan, B.: *Abdominal Operations*, ed. 4, Philadelphia, W. B. Saunders Company, 1926, vol. 2.

43. Judd, E. S., and Hoerner, M. T.: *Surgical Treatment of Carcinoma of the Head of the Pancreas and of the Ampulla of Vater*, Arch. Surg. **31**:937-942 (Dec.) 1935.

44. Wangensteen, O. H.: Cholangitis Following Cholecystenterostomy, Ann. Surg. **87**:54-65 (Jan.) 1928; Pancreatic Cyst, Journal-Lancet **50**:219-224 (May 15) 1930; *Surgical Diseases of the Pancreas, with Special Reference to Cysts, Acute Pancreatic Necrosis, and Hyperinsulinism*, Minnesota Med. **20**:566-576 (Sept.) 1937.



The careful preoperative preparation of the jaundiced patient with vitamin K, bile salts, dextrose, a high carbohydrate diet and, when necessary, vitamin supplements has reduced postoperative complications almost to nothing. When the Quick prothrombin time is normal before operation and is kept so afterward, bleeding is eliminated, and when adequate parenteral dextrose is supplied postoperative hepatorenal insufficiency is not a hazard.

#### SARCOMA OF THE PANCREAS

Sarcoma of the pancreas is rare. Weiss<sup>45</sup> in 1935 estimated that the total number of cases which had been reported in the literature was less than 50. Seeger,<sup>46</sup> in the course of 11,492 collected postmortem examinations, found 2 sarcomas among 132 pancreatic tumors. There was 1 sarcoma in this series of 185 malignant lesions of the pancreas. Sarcoma, which in some cases is radiosensitive, is indistinguishable clinically from carcinoma and is treated similarly.

#### SUMMARY

Surgical lesions of the pancreas are not rare. Two hundred and fifty-five operations on the pancreas were performed at the clinic in a five year period ending in 1939, or approximately 1 operation for every 25 performed on the gallbladder and bile ducts.

The most frequent surgical lesion of the pancreas is carcinoma. One hundred and eighty-five, or 73 per cent, of 255 operations were performed for carcinoma in the five year period. When jaundice is present, an operation that will short-circuit the bile, such as cholecystogastrotomy, is the best procedure. About 15 per cent of lesions which appear to be malignant are in reality benign inflammatory lesions.

Acute pancreatitis is rarely encountered, and when the diagnosis is definite operative treatment is probably best deferred. Chronic pancreatitis is more common and usually is associated with disease of the biliary tract; it can be handled by correction or by treatment of the biliary disease.

Pancreatic cyst, although not common, has been treated surgically in 139 cases at the clinic through 1939. Excision, partial excision and drainage with or without marsupialization have given good results.

Pancreatic stones, when they are not merely calcifications of the parenchyma but real intraductal stones, should be removed to prevent the development of pancreatic atrophy, diabetes and fatty infiltration of the liver.

45. Weiss, S.: *Diseases of the Liver, Gall-Bladder, Ducts and Pancreas: Their Diagnosis and Treatment*, New York, Paul B. Hoeber, Inc., 1935.

46. Seeger, S. J.: *Pancreatic Lithiasis*, Surg., Gynec. & Obst. 40:241-245 (June) 1925.

At the clinic we have observed 16 cases of hyperfunctioning tumor of the islands of Langerhans in which hypoglycemia was present. In 12 of the cases removal of the tumor was possible. Four of the tumors were inoperable carcinomas, and 4 of the 12 removed tumors were carcinomas. Eighteen patients with severe degrees of hypoglycemia were subjected to exploratory laparotomy at the clinic, but no tumor was found. A tumor of the pancreas which produces hypoglycemia should be excised early on account of the danger of malignancy.

Ten cases of accessory pancreas have been observed since 1935. In 6 the accessory pancreas was removed because it was producing symptoms. In 4 the accessory pancreas was removed by excision or some other operative procedure. The accessory pancreas should be removed if it produces symptoms.

Recent advances in the diagnosis of pancreatic disease have been made by virtue of the development of tests for serum amylase and lipase and of the secretin test for stimulation of pancreatic secretion.

# PARALYSIS OF CONJUGATE LATERAL MOVEMENT OF THE EYES IN ASSOCIATION WITH CEREBELLAR ABSCESS

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CINCINNATI

The diagnosis and localization of a cerebellar abscess frequently offer a perplexing problem, and any reliable assistance in its solution is always welcome. In a small series of cases we have found paralysis of conjugate lateral movement of the eyes to the side of the abscess and the frequently associated persistent conjugate deviation of the eyes away from the abscess to be a highly reliable indication of the side of the cerebellum involved. Furthermore, the presence of such paralysis in association with cerebellar disease is strongly suggestive of the presence of an abscess in differentiation from other types of cerebellar involvement, notably neoplasm. Unfortunately such paralysis is not always present in cases of cerebellar abscess, and its absence is of no differential significance.

Disturbance of conjugate movement of the eyes has not commonly attracted much attention in discussions of the symptomatology of cerebellar abscess, although its occurrence has been noted by Rowe,<sup>1</sup> Meyers,<sup>2</sup> Ramadier,<sup>3</sup> de Stella<sup>4</sup> and one of us (Bucy<sup>5</sup>).

Of a series of 7 verified cases of cerebellar abscess, we have noted paralysis of conjugate lateral movement of the eyes to the side of the lesion in 3.

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From the Division of Neurosurgery, University of Chicago.

1. Rowe, S. N.: The Use of Sulfanilamide in the Treatment of Brain Abscess, *Ann. Surg.* **107**:620-626, 1938.

2. Meyers, I. L.: Conjugate Deviation of the Head and Eyes: Its Value in Diagnosis and Localization of Abscess of the Brain, *Arch. Otolaryng.* **13**:683-708 (May) 1931.

3. Ramadier, J.; Caussé, R.; André-Thomas; Barré, J. A., and Velter, E.: Les abcès du cervelet, *Rev. d'oto-neuro-ophth.* **13**:1-106, 1935.

4. de Stella, H.: Deux signes importants du syndrome cérébelleux pour le diagnostic de l'abcès cérébelleux: Les troubles du langage et les paralysies oculaires, *Ann. d'oto-laryng.*, 1938, pp. 535-537.

5. Bucy, P. C.: Sulfanilamide in the Treatment of Brain Abscess and Prevention of Meningitis, *J. A. M. A.* **111**:1639-1641 (Oct. 29) 1938.

## REPORT OF CASES

*CASE 1.*—*Patient a girl aged 11 months; pneumonia at 17 days; vomiting and stupor ten months later; enlarged head; papilledema; deviation of the eyes to the left, with paralysis of conjugate movement to the right; ptosis of the left upper eyelid; absence of right corneal reflex; slight weakness of the left facial nerve; positive Babinski sign on the left; cerebellar abscess on the right side; drainage; recovery.*

*History.*—B. S., a girl aged 11 months, was referred by Dr. Joseph Brenne-  
mann, of the Children's Memorial Hospital, with a tentative diagnosis of intra-  
cranial neoplasm. Her delivery and early development had been normal and  
uneventful until the seventeenth postnatal day, when she contracted pneumonia and  
was hospitalized for two weeks. One month later she vomited all feedings for a  
time, but this difficulty disappeared after a change of formula, and she appeared  
quite well until three weeks before admission, except that she never sat up unsup-  
ported. During the three weeks preceding admission there was another episode  
of vomiting, which was apparently controlled by another change in formula.  
During this period she had become stuporous but awakened three to four times  
nightly and cried in a whining tone. On one occasion the mother noticed that  
the right eye turned inward and down. She was admitted to the University of  
Chicago Clinics on Nov. 28, 1931.

*Examination.*—Physical examination on admission revealed her to be irritable  
and whining. She tended to lie on her back, moving very little when undisturbed.  
Her temperature was 37.4 C. (99.3 F.). The red blood cell count was 6,180,000  
per cubic millimeter; the white blood cell count was 13,900 per cubic millimeter,  
and the value for hemoglobin was 70 per cent. The urine was normal. The child  
was obviously underweight and malnourished. The head measured 47.3 cm. in its  
occipital-frontal circumference and seemed tender to palpation. Macewen's sign  
was present. The head usually was turned to the right, and any movement of it  
seemed to elicit pain. The Kernig and Brudzinski signs were negative. There  
was 1 to 2 D. of choking of each optic disk, and there was definite atrophy of the  
optic nerves. Both eyes were diverted downward and to the left but occasionally  
looked straight ahead, never beyond the midline to the right. The pupils were  
equal and regular but did not react to light. However, a mydriatic had been  
instilled prior to admission. There was ptosis of the left upper eyelid. The right  
corneal reflex was absent, and there was a slight droop of the left corner of the  
mouth. Otherwise the cranial nerves were normal. The legs did not seem to move  
voluntarily. There was no spasticity or hypotonia. The abdominal reflexes were  
absent. The tendon reflexes were not increased and were bilaterally equal. There  
was a positive Babinski sign on the left side, and on the right the sign was equivocal.

On November 30 spasticity of the legs had developed. A diagnosis of internal  
hydrocephalus possibly resulting from a tumor in the cerebellar fossa was made,  
and on December 1 Dr. Percival Bailey made a ventriculogram. This showed  
hydrocephalus of the lateral and third ventricles and nonfilling of the fourth  
ventricle.

On December 2 the cerebellum was exposed. An incision was made in the  
dura mater over the left cerebellar hemisphere, and as it was being carried across  
the midline pus was encountered. This was found to be coming from the region  
of the vermis. The main abscess cavity, however, was found deep in the right  
cerebellar hemisphere. It was filled with thick white pus, which was aspirated.  
The cavity was enormous, occupying almost the entire right cerebellar hemisphere

and the vermis and extending somewhat to the left of the midline. It extended as far forward as one could see. The cavity was drained, and the wound was closed. Fortunately no organisms could be cultured from the pus.

Drainage continued for some time, after which the wound healed spontaneously. The patient was discharged on Feb. 3, 1932. At discharge there was marked bilateral atrophy of the optic nerve; the extraocular movements were full; the right corneal reflex was absent, and there was hypalgesia over the distribution of the right fifth cranial nerve.

The child has been followed in the outpatient service at intervals. Her vision has remained considerably impaired. On Oct. 16, 1939, vision in the right eye was 3/200, and in the left, 4/10 with glasses. No weakness, ataxia, incoordination of movement or definite hypotonia has been noticed. No nystagmus has been seen at any time. A slight right internal strabismus has persisted. On July 14, 1938 her intelligence quotient was 80 by the Stanford-Binet test.

*Comment.*—The disturbance of lateral conjugate movement of the eyes observed in this case would now cause us to consider cerebellar abscess as the most likely diagnosis and to localize the lesion in the right cerebellar hemisphere. Correct evaluation of this sign would have reduced the extent of the operation materially and would have prevented an unnecessary ventriculographic examination.

Unfortunately, a record is not available as to when the paralysis of conjugate movement disappeared. It was no longer present when the patient was discharged, two months after the operation.

*CASE 2.*—*Patient a girl aged 4 years; March 7, 1938 brief attack of pain in the right ear; March 29, severe headache and vomiting; admitted to the hospital April 3; semistuporous; head retracted; papilledema; eyes deviated to the left with paralysis of conjugate movement to the right; bilateral Babinski sign; infrequent voluntary movement of the right arm, hypotonia of the left arm and spasticity of the right extremities; ventricular drainage followed four days later by evacuation of the abscess and sulfanilamide therapy; complete recovery.*

F. S., a girl 4 years of age, was referred to the University of Chicago Clinics by Dr. Joseph Brennemann, of Chicago. She was admitted on April 3, 1938. On March 7 she had complained of pain in her right ear. This soon subsided, and she was well until March 29, when she had a severe headache and vomited. These symptoms continued, and she soon grew weak and unable to walk. Examination of the spinal fluid at the Children's Memorial Hospital, Chicago, on April 2 revealed 60 lymphocytes per cubic millimeter.

Examination on April 3 at the University of Chicago Clinics revealed the child to be semistuporous. Her head was retracted, and there was marked suboccipital tenderness. There was definite early papilledema. The pupils were dilated and reacted poorly to light. The eyes were deviated to the left, and it was impossible to get her to move them to the right of the midline. The tendon reflexes were active throughout, although they were somewhat brisker on the right side. There was an unsustained ankle clonus on the left, and Babinski's sign was present bilaterally. Pinprick was appreciated equally everywhere. The right arm was moved infrequently, whereas the left arm and the legs were moved freely. There was definite hypotonia of the left and some spasticity of the right extremities.

Because of her precarious condition, one lateral ventricle was punctured on April 3, and a T-shaped needle was left in place to provide continuous drainage.

Immediately thereafter her condition improved markedly. She became alert and talked readily and coherently. However, the conjugate deviation of the eyes to the left or occasionally to the left and upward, with inability to move the eyes beyond the midline to the right, persisted. The other signs did not change except that she became able to move all four extremities, all of which were ataxic, the right ones most markedly so.

By April 7 her condition had improved sufficiently to permit a direct attack on the cerebellar lesion. A cerebellar exploration disclosed a large abscess in the right cerebellar hemisphere. Subsequent culture of the pus yielded a heavy growth of hemolytic streptococci.

With a single aspiration of the abscess and subsequent sulfanilamide therapy she improved rapidly and was soon discharged from the hospital. She has remained well.

The paralysis of conjugate deviation of the eyes to the right persisted for twenty-four hours after aspiration of the abscess and then rapidly disappeared. By the afternoon of April 9 the ocular movements were of full range and there was no nystagmus.

*Comment.*—As was noted in detail in our previous report of this case,<sup>5</sup> considerable difficulty was experienced in differential diagnosis, and the operative procedure was unnecessarily extensive. Full realization of the significance of the paralysis of conjugate deviation would undoubtedly have spared the patient and us much of this. Fortunately, however, we were learning by experience, and when the same condition was seen in the third case its significance was promptly recognized and fully utilized.

*CASE 3.*—*Patient a boy aged 8 years; March 1940 sore throat, followed by earache, headache on the right side, vomiting, lethargy and incoordination of the right extremities; admitted to the hospital April 3; semistuporous; slow pulse and respiration; papilledema; paralysis of conjugate lateral movement of the eyes to the right; hypotonia and ataxia of the right arm and leg; diagnosis, abscess of the right cerebellar hemisphere; drainage of the abscess; complete recovery.*

*History.*—A. D., a boy aged 8 years, was referred to the University of Chicago Clinics by Dr. M. G. Peterman, of Milwaukee. He had been well until four weeks before admission, on April 3, 1940. Early in March he had an acute febrile illness and a sore throat. He was confined to bed for one week and then was up and about for one week, after which time he began to complain of earache and headache on the right side and vomited several times. The ear never discharged, but as he continued to have fever, headache and vomiting he was admitted to the Milwaukee Children's Hospital on March 26, under Dr. Peterman's care. There his temperature remained normal after two days, but he became increasingly lethargic and showed progressive incoordination of the movements of the right extremities. Repeated lumbar punctures showed an increase of cells in the spinal fluid (up to 283), but no organisms grew on culture. The sugar content of the spinal fluid ranged from 57 to 72 mg., and the total protein content from 65 to 110 mg. per hundred cubic centimeters. He received 30 grains (1.8 Gm.) of sulfanilamide for the two days preceding transfer to the University of Chicago Clinics (April 3) with the diagnosis of cerebellar abscess.

*Examination.*—When first seen, at 4:30 p. m. on April 3, the patient was lying flat in bed. He appeared extremely lethargic but could be roused enough to



Rowe<sup>1</sup> reported 2 cases of such paralysis. Guthrie<sup>7</sup> stressed the importance of deviation of the eyes away from the side of the lesion, although he did not notice it in his case until the day following the operation. De Stella<sup>4</sup> also presented the paralysis as an important diagnostic aid. Meyers,<sup>2</sup> who discussed this problem at some length, was able to present much less in the way of definitive evidence. In all of his 7 cases there occurred more or less conjugate deviation of the eyes away from the side of the lesion, but he was unable to make any statement relative to paralysis of conjugate movement toward the side of the lesion, as 5 of his patients were stuporous when admitted and in 2 instances no mention was made of the presence or absence of such paralysis.

There appears to be but little doubt that the ipsilateral paralysis of conjugate lateral movement of the eyes which occurs in some cases of cerebellar abscess does not result from a lesion of the cerebellum per se. There is no experimental evidence which would indicate that a cerebellar lesion is capable of producing such paralysis. Botterell and Fulton<sup>8</sup> found in the monkey no disturbance of conjugate ocular movement following a lesion of the vermis, the cerebellar hemisphere or the deep nuclei (dentate, fastigial, globose or emboliform), and Dow<sup>9</sup> found no disturbance of ocular movements subsequent to a lesion of the uvula, nodulus or parafocculus in primates. It is true, of course, that several investigators, including Horsley and Clarke,<sup>10</sup> Ferrier<sup>11</sup> and Mussen,<sup>12</sup> elicited movements of the eyes by electrical stimulation of several parts of the cerebellum. However, more recently Clarke,<sup>13</sup> elaborating on previous investigations, concluded that all ocular movements so obtained were probably due to spread of the current to deeper nuclei and to extracerebellar tissues, although unreported investigations by Denny-Brown, Walker and Botterell on the electrical excitability

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7. Guthrie, D.: Cerebellar Abscess in Childhood, *J. Laryng. & Otol.* **46**:604-611, 1931.

8. Botterell, E. H., and Fulton, J. F.: Functional Localization in the Cerebellum of Primates: II. Lesions of Midline Structures (Vermis) and Deep Nuclei, *J. Comp. Neurol.* **69**:47-62, 1938; III. Lesions of Hemispheres (Neocerebellum), *ibid.* **69**:63-87, 1938.

9. Dow, R. S.: The Relation of the Parafocculus to the Movement of the Eyes, *Am. J. Physiol.* **113**:296-298, 1935; Effect of Lesions in the Vestibular Part of the Cerebellum in Primates, *Arch. Neurol. & Psychiat.* **40**:500-520 (Sept.) 1938.

10. Horsley, V., and Clarke, R. H.: The Structure and Functions of the Cerebellum Examined by a New Method, *Brain* **31**:45-124, 1908.

11. Ferrier, D.: The Functions of the Brain, ed. 2, London, Smith Elder & Co, 1886.

12. Mussen, A. C.: Experimental Investigations on the Cerebellum, *Brain* **50**:313-349, 1927.

13. Clarke, R. H.: Experimental Stimulation of the Cerebellum, *Brain* **49**:557-569, 1926.



of the cerebellum indicate some definite influence of the cerebellum on ocular movements not resulting from spread of current. As Bailey, Buchanan and Bucy<sup>14</sup> have pointed out, paralysis of conjugate lateral movement of the eyes is rare in cases of cerebellar neoplasm, although, as will be noted more fully later, it has been recorded (Brain<sup>15</sup>). In addition, the observation that in cases of cerebellar abscess the paralysis disappears rapidly (in twenty-four to forty-eight hours) after the abscess has been evacuated and the pressure relieved indicates that the paralysis arises not as a result of damage to the cerebellum but rather in consequence of pressure on some neighboring structure. The fact that, in contrast with cerebellar tumor, tumor of the pons is commonly associated with such paralysis in the absence of any increased intracranial pressure (Bailey, Buchanan and Bucy;<sup>14</sup> Brain;<sup>15</sup> Bramwell<sup>16</sup>) would indicate that the pons is probably the part of the brain concerned with this paralysis. Exactly what nucleus or fiber system in the pons must be involved to give rise to paralysis of conjugate lateral movement of the eyes is not clear, but it seems likely that the sixth nucleus and the posterior longitudinal bundle connecting it with the other oculomotor nuclei are apt to be the structures concerned, as one of us (Bucy<sup>5</sup>) postulated. This seems particularly likely in view of the observations of Ferraro and Barrera<sup>17</sup> that a lesion of Deiters' nucleus or of some other vestibular nucleus does not result in disturbances of coordinated movements of the eyes, whereas such disturbances do arise when the posterior longitudinal bundle is implicated. This, of course, is contrary to the idea of Bruce,<sup>18</sup> who attributed these disturbances to damage of Deiters' nucleus.

The clinical implications of this phenomenon in patients suspected of being the victims of cerebellar abscesses are threefold: (1) lateralization of the lesion within the cerebellum, (2) localization of the abscess to the cerebellum and (3) differentiation of abscess from tumor.

There seems to be little doubt both from our own experience and from the literature that paralysis of conjugate lateral movement of the eyes produced by a lesion in the posterior fossa is always ipsilateral to the lesion. This is true regardless of whether the lesion is cerebellar,

14. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: *Intracranial Tumors of Infancy and Childhood*, Chicago, University of Chicago Press, 1939.

15. Brain, W. R.: On the Rotated or "Cerebellar" Posture of the Head, *Brain* 49:61-76, 1926.

16. Bramwell, B.: *Intracranial Tumours*, Edinburgh, Young J. Pentland, 1888.

17. Ferraro, A., and Barrera, S. E.: Differential Features of "Cerebellar" and "Vestibular" Phenomena in Macacus Rhesus, *Arch. Neurol. & Psychiat.* 39:902-918 (May) 1938.

18. Bruce, A.: The Localization and Symptoms of Disease of the Cerebellum Considered in Relation to Its Anatomical Connections, *Tr. Med.-Chir. Soc. Edinburgh* 18:85-97, 1899.

pontile or extraneural. Thus, in the case of cerebellar abscess paralysis of conjugate movement of the eyes to the right lateralizes the abscess to the right cerebellar hemisphere.

The other implications of such paralysis, though not so positive, are nevertheless of great diagnostic value when considered in the light of the history of the disease and the other findings on examination. It is well established that cerebral disease of either the occipital or the posterior parts of the frontal lobes, or of their projection systems, may produce weakness or paralysis of conjugate lateral movement of the eyes to the side opposite the lesion (Holmes<sup>19</sup>). However, it is also well known that such paralysis is commonly transitory, regardless of whether the pathologic condition is relieved, and that it is rarely seen except with an acute lesion, such as a cerebrovascular accident or a surgical wound. Dandy<sup>20</sup> has remarked that he has never seen such paralysis arise as the result of a neoplasm except when the brain stem was involved. Accordingly, in those cases in which an abscess is suspected, paralysis of conjugate lateral movement of the eyes is strongly suggestive of location of the abscess in the cerebellum. Furthermore, Holmes<sup>19</sup> has pointed out that, unlike the complete paralysis which we have observed in cases of cerebellar abscess, the paralysis arising from a lesion of the frontal lobe, although apparently complete so far as the response to command is concerned, is not complete when the patient is asked to follow with his eyes a slowly moving object. Furthermore, if there are two marks on a sheet of paper the patient may be unable to turn his eyes from one to the other, but he can often do so when the marks are joined by a line. The movements in the latter instance apparently are accomplished via the occipital cortical innervation. Such differences in the paralysis do not obtain when the lesion involves the pontile mechanism, which is more peripheral and less specialized.

It should also be pointed out, as has been done by Eagleton,<sup>21</sup> that when an abscess is believed to have arisen as a result of infection in the ear the problem in localization is generally between the cerebellum and the temporal lobe. Here paralysis of conjugate lateral movement of the eyes will be of great value, as it has never been known to result from a lesion in the temporal lobe.

Paralysis of conjugate lateral deviation of the eyes is also of value in differentiating cerebellar abscess from a neoplasm in the posterior fossa. In this clinic we have never observed paralysis of this type from a cere-

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19. Holmes, G.: *The Cerebral Integration of the Ocular Movements*, Brit. M. J. **2**:107-112, 1938.

20. Dandy, W.: *The Brain*, in Lewis, D.: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1934, vol. 12, chap. 1.

21. Eagleton, W. P.: *Brain Abscess: Its Surgical Pathology and Operative Technique*, New York, The Macmillan Company, 1924.

bellar tumor either in a child or in an adult. And such observations appear to have been made but rarely by others. Brain<sup>15</sup> recorded 1 well verified case (case 12) in which a cystic tumor of the right cerebellar hemisphere resulted in a weakness of conjugate movement of the eyes to the right. In contrast to our experience with abscesses, the paralysis was not complete. Bruns<sup>22</sup> also referred to such ipsilateral paralysis from cerebellar tumors, but in his report details are lacking and verification uncertain. Bruce<sup>18</sup> discussed such paralysis from cerebellar lesions but did not note the nature of the lesions under consideration. Stewart and Holmes<sup>23</sup> remarked that paralysis of conjugate lateral movement of the eyes is frequently seen with both intracerebellar and extracerebellar tumors but, unlike the finding in our cases of abscess, the paralysis was "*never in complete degree.*" They stated, furthermore, that it was more prevalent with the extracerebellar tumors. It would thus appear that paralysis of conjugate movement of the eyes, particularly when severe or complete, is far more suggestive of a cerebellar abscess than of a cerebellar tumor.

We have observed a weakness of conjugate lateral movement of the eyes in only 1 of our cases of acoustic neurinoma, and in that instance there were no diagnostic difficulties. Cushing<sup>24</sup> recorded having seen such a disturbance on several occasions, and Oppenheim,<sup>25</sup> Stewart and Holmes<sup>23</sup> and others have made similar observations. Rarely, however, will the differentiation of acoustic neurinoma and cerebellar abscess prove difficult. The same may be said of pontile glioma, with which this phenomenon is even more common (Bailey, Buchanan and Bucy;<sup>14</sup> Brain;<sup>15</sup> Dandy;<sup>20</sup> Bramwell<sup>16</sup>). We have, however, observed 1 unusual case of pontile glioma associated with paralysis of conjugate lateral movement of the eyes in which a diagnosis of cerebellar abscess was erroneously made. As evidence that, although useful, this sign cannot be considered pathognomonic of cerebellar abscess in cases in which an abscess is suspected, the history of that case is appended.

CASE 4.—*Patient a woman aged 35 years; February 1931, severe left earache; headache on the left side; purulent discharge from the left ear; apparent recovery; July 1931, severe headache followed by staggering gait; August 1931, vomiting; operation for intestinal obstruction; no relief; September 15, stiff neck; stupor September 23, admitted to the hospital; semicomatose; fever; tachycardia; papilledema; paralysis of conjugate lateral movement of eyes to the left; nystagmus;*

22. Bruns, L.: Die Geschwülste des Nervensystems, Berlin, S. Karger, 1897.

23. Stewart, T. G., and Holmes, G.: Symptomatology of Cerebellar Tumours: A Study of Forty Cases, Brain **27**:522-591, 1904.

24. Cushing, H.: Tumours of the Nervus Acusticus and the Syndrome of the Cerebello-Pontine Angle, Philadelphia, W. B. Saunders Company, 1917.

25. Oppenheim, H.: Ueber mehrere Fälle von endocraniellen Tumor, in welchen es gelang, eine genauere Localdiagnose zu stellen, Berl. klin. Wchnschr. **27**:38-40, 1890.

*rapid to the right, slow and coarse on attempting to look to the left; weakness of the left facial nerve; hypalgesia of the right half of the body; hypotonia and ataxia of the left extremities; clouding of the left mastoid on roentgen examination; diagnosis, abscess of the left side of the cerebellum; operation, no abscess found; death December 23; necropsy diagnosis, glioma of the left side of the pons.*

E. N., a woman 35 years of age, was referred to the University of Chicago Clinics by Dr. E. Grimm, of Chicago. She was admitted on Sept. 23, 1931, in a semicomatose condition.

The following history was elicited from her parents: She had been well until February 1931, when she had a severe earache on the left side, associated with a severe headache. The tympanic membrane ruptured spontaneously, and pus was discharged, giving the patient relief. The discharge continued for a few weeks and then subsided. She had no complaints until July, when she again complained of severe headache. About the middle of July she had difficulty in walking and staggered as though intoxicated. These symptoms progressed, and by the middle of August she began to vomit. As a result she was operated on for intestinal obstruction, which was attributed to adhesions at the site of a previous appendectomy. This operation, however, provided no relief. About September 15 the neck became stiff, with the head somewhat rotated. She suffered from chills. Her temperature was not taken. She gradually became more stuporous, became unable to take food and was incontinent.

On admission she was semicomatose. The temperature ranged from 38.4 to 39.6 C. (101 to 103 F.), the pulse rate from 140 to 160 and the respiratory rate from 20 to 26. The head was flexed and rotated with the face to the left. Pressure in the left suboccipital region was painful. There was a purulent discharge from the left ear. The heart, lungs and abdomen presented no abnormality except for the tachycardia and the surgical incisions. The blood pressure was 126 systolic and 90 diastolic. The right pupil was larger than the left, and only the right responded to light. There was a marked bilateral papilledema. Conjugate deviation of the eyes to the right could be obtained, but several examiners were unable to get the patient to move her eyes to the left beyond the midline. There were a rapid nystagmus on looking to the right and a coarse slow nystagmus on attempting to look to the left. There was weakness of the left facial nerve, of the peripheral type. There was apparent hypalgesia of the entire right half of the body. The left extremities were hypotonic. The movements of the left arm were ataxic. The abdominal reflexes were absent on the right side. The tendon reflexes were all abolished, and Babinski's sign was not obtainable.

The white blood cell count was 14,800 per cubic millimeter. The Wassermann and Kahn reactions of the blood were negative. Roentgen examination revealed a normal right mastoid process, but on the left side there were dense sclerosis of the bone about the antrum and clouding of some of the mastoid cells.

*Diagnosis.*—In view of the otitic infection and the evidence of involvement of the left cerebellar hemisphere, the cranial nerves in the left cerebellopontile angle and the left side of the brain stem, it was felt that she was suffering from an abscess of the left cerebellar hemisphere.

*Operation.*—On September 24 a unilateral suboccipital exploration was carried out on the left. There was a marked increase of intracranial pressure. No abscess was found. A small decompression was provided, and the wound was closed.

*Postoperative Course.*—Subsequently she improved. The notes available are not detailed, but apparently conjugate deviation of the eyes to the right was still present when she was discharged from the hospital, on October 21.

In the latter part of November her symptoms of headache and vomiting returned. She became lethargic and had increasing difficulty in walking. She was readmitted on December 14. At that time conjugate lateral movements of the eyes were possible to either side and, though limited in range, were equal on the two sides. Other findings gave adequate evidence of a lesion in the left cerebellopontile angle. At operation, on December 22, a large glioma (polar spongioblastoma) of the left side of the pons, extending laterally along the seventh and eighth nerves into the internal auditory meatus, was disclosed. She died the following day, and necropsy confirmed the operative findings.

#### SUMMARY AND CONCLUSIONS

Of 7 cases of cerebellar abscess, ipsilateral paralysis of conjugate lateral movements of the eyes occurred in 3. From the study of these cases and a review of the pertinent literature it is concluded that:

1. The paralysis probably arises as a result of compression of the pons, with implication of the abducens nucleus and the posterior longitudinal bundle.

2. In cases of cerebellar or pontile involvement the paralysis is always toward the side of the lesion.

3. In cases in which an intracranial abscess is suspected, such involvement points strongly toward the cerebellum as the site of the lesion.

4. When the differentiation lies between cerebellar abscess and intra-cerebellar tumor, such paralysis of ocular movement, particularly when it is severe, is strongly in favor of a diagnosis of abscess. When an acoustic neurinoma or a pontile glioma is suggested, the significance of such paralysis as to the nature of the lesion is greatly reduced.

## INSTRUMENTAL PERFORATION OF THE RECTOSIGMOID

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It must be a very disturbing experience for a physician to find that he has perforated the bowel with a sigmoidoscope. Imagine the sensation of the physician who is reported by Lockhart-Mummery to have looked into his instrument and found himself gazing at the gallbladder! This operator's dismay would have been no less if the perforation had occurred with a bougie or a dilator, for whether the accident happens during diagnostic or therapeutic efforts the intention has been to help the patient, yet harm has resulted. For this reason the subject deserves careful study and analysis.

There are many other causes of penetration of the bowel by an object inserted through the anus, some of which have been known for centuries. The code of Hammurabi states that impalement by "sitting on a stick" will be the punishment for lustful murder. Torture by this means was a common practice in some oriental countries. Murder without signs of external violence was accomplished by this means, and it is said that Edward II of England was killed in this way. Ignorance and superstition in self treatment, ribaldry in "practical jokes" (e. g., with compressed air), sadism or sexual perversion (anal eroticism) may all lead to perforation of the sigmoid flexure of the colon. A fall on an upright object may result in impalement, since the conelike shape of the pelvis leads the object into the rectum. The commonest instance of this is in children who slide down a hay stack and land on the handle of a pitchfork. These causes account for most transanal perforations of the sigmoid, and fortunately the accidents from therapeutic procedures are rare.

The members of the surgical staff of this institution have observed 8 cases of perforation of the bowel from a foreign body inserted through the anus (fig. 1). In 4 of these the perforation was caused by the sigmoidoscope; in 2 by an enema tip, and in 1 each by an electrode and a thermometer. The events leading up to the perforation are reported

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as accurately as possible, but it must be remembered that they are reviewed in retrospect from records and conversation and not from personal observation, so they may not include all details.

## REPORT OF CASES

CASE 1.—J. C., a 60 year old man, had several severe hemorrhages from the rectum at the time of bowel movement. Hemorrhoids had been present for one

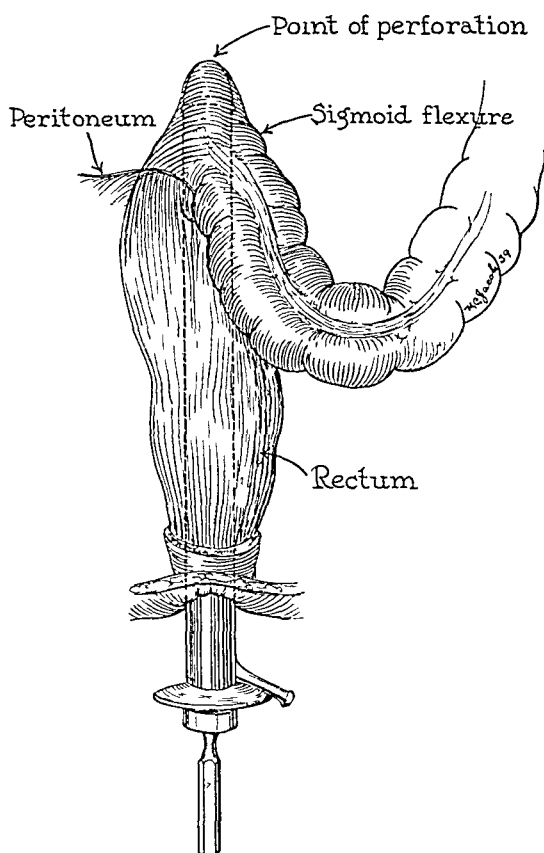


Fig. 1.—Hard rubber nozzle which punctured the normal sigmoid of a conscious patient during self administration of a "high enema." There was not enough pain to warn the patient of his danger.

year, but on examination a bleeding point from this source could not be detected. A barium sulfate enema showed a slight delay in filling in the rectosigmoid, so a sigmoidoscopic examination was decided on.

A caudal anesthetic was given. The sigmoidoscope was inserted by maneuver to about 20 cm., at which point a sudden loss of resistance was felt. The stilet was withdrawn and the light attached. The examiner could see intra-abdominal contents and realized at once that penetration of the bowel had occurred. He

called a surgical consultant, who performed a laparotomy immediately. Very little soiling of the peritoneal cavity had occurred from a perforation 1.5 cm. in diameter on the anterior (antimesenteric) surface of the rectosigmoid. The opening was sutured with silk, and the abdomen was closed without drainage. Uneventful recovery followed.

CASE 2.—H. B., a man of 54 years, complained of "piles," bleeding from the bowel, ribbon-like stools and loss of weight. There was severe secondary anemia, and blood was present in the stools. Roentgen examination showed no lesion of the upper part of the gastrointestinal tract. Internal hemorrhoids could be felt on digital examination, but no mass could be palpated. Sigmoidoscopic examination was decided on. A caudal anesthetic was used for the examination and, as nearly as could be determined, the sigmoidoscope was inserted about 18 cm. before the light was attached. On first looking into the instrument the examiner said that he thought he saw material resembling omentum, but it could not be found again, nor could a perforation be seen, so the patient was observed for eight hours before a consultation was obtained. At this time distention of the abdomen with pneumoperitoneum and obliteration of the hepatic dulness was present. There were tenderness and spasm in the lower part of the abdomen, so perforation of the bowel was evident. At laparotomy no fecal material was found in the peritoneal cavity, but there was about 100 cc. of thin, purulent material in the pouch of Douglas. A tear  $\frac{3}{4}$  inch (1.9 cm.) long on the anterior surface of the rectosigmoid was sutured. The patient had an uneventful convalescence for seven days, and then intestinal obstruction developed from attachment of a loop of ileum to the scar. He died suddenly a few hours after the release of this obstruction. Postmortem examination showed a pulmonary embolus to have caused death. The wound in the sigmoid was firmly healed.

CASE 3.—R. A., a 57 year old woman with syphilis, tabes dorsalis and secondary anemia, complained of loss of weight, diarrhea and bleeding from the bowels. Roentgen examination of the gastrointestinal tract, including a barium sulfate enema, failed to show an adequate cause for her symptoms. No parasites were found in the stool. Examination with a short proctoscope revealed ulcers high in the rectum that resembled those of ulcerative colitis; so sigmoidoscopic examination was desired to confirm the diagnosis and take material for cultures. The exact details of the sigmoidoscopy are not clear, but apparently the instrument was inserted by maneuver, after which the bowel was dilated with a hand bulb before the lesions were inspected. No evidence of perforation was noted at the time, nor did the patient complain of any pain; so the accident was unsuspected. An hour later she experienced severe generalized abdominal pain, and examination revealed pneumoperitoneum associated with spasm and tenderness of the abdominal muscles. A diagnosis of perforation of the bowel was made and confirmed by a surgical consultant, who arranged for an immediate laparotomy. Nitrogen monoxide and oxygen anesthesia was being induced when the patient stopped breathing. She had shown no sign of vomiting but had apparently aspirated vomitus, for it ran out of her nose when the head was lowered. Immediate direct laryngoscopy with suction failed to clear the airway, and she died.

Autopsy showed aspirated food in the bronchi and a perforation of the rectosigmoid. The latter occurred in a diseased, weakened part of the wall and might



have been from rupture by air pressure but appeared to have been caused by the sigmoidoscope.

CASE 4.—J. G., a 58 year old man with a condition diagnosed as ulcerative colitis, was having twenty or thirty stools a day. Sigmoidoscopy was done under caudal anesthesia to confirm the diagnosis and to obtain material for cultures. The instrument was inserted by maneuver, and the examiner noted that it tended to swing to the right, which caused some difficulty in its insertion. After it was in place the light bulb burned out; so the instrument was withdrawn until the bulb was changed. After this the examination was uneventful, and no perforation of the bowel was seen. However, two and one-half hours later, as the patient was attempting to void urine, he was seized with a sharp crampy pain in the lower part of the abdomen, accompanied with a chill and sweating. Examination showed pallor and shock, with a pulse rate of 140 per minute; the blood pressure was 70 systolic and 50 diastolic, and the abdomen was tender and rigid. A surgical consultant advised operation after parenteral fluids and blood had been given. Operation revealed cloudy fluid with a fecal odor in the peritoneal cavity, but no perforation of the bowel could be found. Because of the patient's poor condition a prolonged search was not made. Drains were inserted into the pelvis, and the wound was closed. Death followed in forty-eight hours. Autopsy showed general peritonitis, ulcerative colitis and a perforation of the rectosigmoid on the left side of its antimesenteric border.

CASE 5.—M. P. O'B., a 71 year old man with generalized arteriosclerosis, was under medical supervision for a duodenal ulcer. He was seized with an excruciating pain in the abdomen, which was thought to be due to the perforation of his ulcer. At operation, three hours later, general peritonitis from perforation of the sigmoid was found. The perforation was closed, and a colostomy was done.

After the operation, by direct questioning it was found that the patient had given himself an enema just before the onset of his pain. He had not mentioned this before because it did not occur to him that it was related to his illness. Apparently he perforated the sigmoid at that time.

His postoperative course was unsatisfactory, and in spite of fluids, transfusion and other supportive measures he died sixteen hours after operation.

CASE 6.—H. V. C., a 69 year old man, had been constipated for years and had taken frequent enemas for this condition. He was told by a friend that "high" enemas were more effective; so he purchased at a drug store a long, hard rubber tip to give himself a "high" enema. Actually he received a douche nozzle (fig. 2). He found this rather hard to insert, but he passed it up to the hilt and allowed a quart (0.9 liter) of soapsuds solution to flow in. He was immediately seized with generalized abdominal pain and collapsed. A physician found abdominal rigidity, tenderness and rebound tenderness with obliteration of the hepatic dulness. He recognized the cause of the accident and had the patient moved to the hospital at once. Operation was done in less than two hours after the accident.

The peritoneal cavity was found to contain turbid, soapy fluid, which was carefully aspirated from all pockets. The peritoneal surfaces were inflamed by the chemical irritation. A perforation 1 inch (2.5 cm.) long was found on the

anterior surface of the lower part of the sigmoid. It was closed by two layers of silk sutures. Recovery was *uneventful except for severe paralytic ileus* during the first five days after the operation.

CASE 7.—A 39 year old man was referred to the clinic for treatment of syphilis of the central nervous system with dementia paralytica. After thorough physical and laboratory examinations he was considered to be a suitable candidate for general hyperthermia. This treatment necessitated accurate, continuous readings of the patient's temperature, which were obtained by means of a thermo-

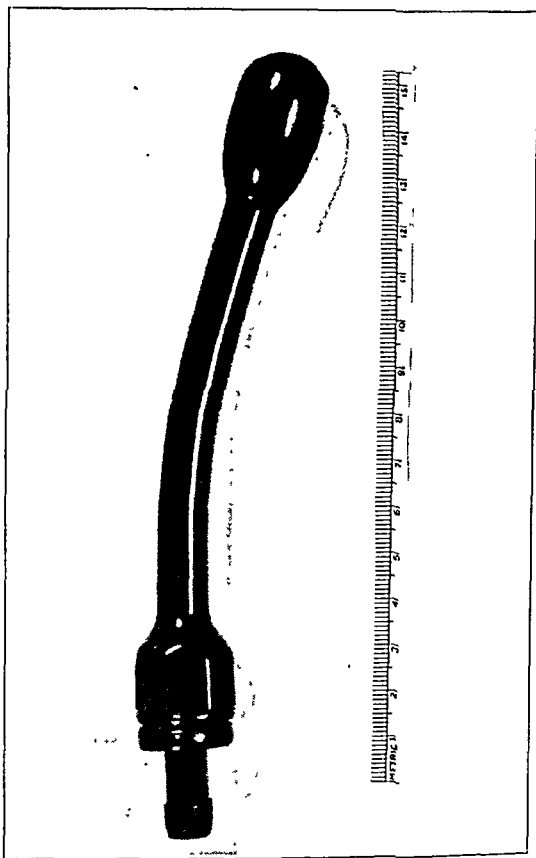


Fig. 2.—Point of perforation of the sigmoid, on the anterior surface, just above the peritoneal reflection, where the instrument may go into a blind pouch.

couple in the rectum. The patient was difficult to handle, owing to a manic type of excitation. Restraint and large doses of paraldehyde were necessary to control him. The first two hyperthermia treatments, given at monthly intervals, were difficult for the attendants but were otherwise uneventful. After the third treatment high fever resulted and death followed. At autopsy a perforation of the rectum was discovered. Apparently the rectal thermometer had penetrated the bowel during the patient's disoriented state. It is difficult to see how this could have been prevented under the circumstances.

CASE 8.—A. H., a 20 year old man, had general polyposis of the colon, of the familial type. The surgeon in charge of his case was fulgurating the rectal polyps in preparation for ileosigmoidostomy with colectomy. At the time of the accident, about 50 polyps had been removed when the operator saw a small opening in the bowel wall where one of the tumors had been cauterized. He promptly opened the abdomen and closed the perforation of the rectosigmoid. The patient made an uneventful recovery.

#### COMMENT

Perforation of the sigmoid during diagnostic or therapeutic procedures is probably a very rare accident. Little has been written about it, but of the papers published, those by Crohn and Rosenak and Ménégauz are the most complete. The remainder of the literature, as far as could be found, consisted of case reports or a brief mention in textbooks. Yet from a study of the material available some conclusions can be drawn.

It is apparent that the normal bowel of the conscious patient may be perforated without much pain or the use of excessive force. Crohn and Rosenak attested this. My experience verifies it, for 2 of the patients punctured the sigmoid with blunt, hard rubber tips without realizing that they had done any harm until an enema flooded the peritoneal cavity. If the normal bowel can be perforated so easily, then the hazard is much greater with ulceration and disease, for the weakened wall may be ruptured by the air pressure from a hand bulb, punctured with a bougie or a dilator or perforated with a sigmoidoscope. The ease with which these accidents can happen is not generally appreciated. A legal opinion is on record exonerating a physician from blame under these circumstances. The verdict of the coroner was "death from general peritonitis following perforation of the lower part of the intestine caused by the use of an instrument by a competent person for the necessary examination in dysentery, and death was due to misadventure" (*Fatal Use of the Sigmoidoscope*, Foreign Letters [London], *J. A. M. A.* 78: 829 [March 18] 1922).

In all the cases of perforation with the sigmoidoscope reported here the accident followed blind insertion of the instrument by maneuver. This is a bad procedure. The instrument was made to look through, so one should see where it is going. Little is said of this in the literature, but some authors, particularly Buie, have stressed its importance. The same principle of instrumentation under direct vision should apply to the use of bougies or dilators for high rectal strictures. After the sphincter muscle is passed, visual guidance of an instrument is the only safe method.

Anesthesia was used in 4 of these cases, and in 2 others the patients had syphilis of the central nervous system with probably diminished sensation. This is a factor of doubtful significance in contributing to the perforation. If anesthesia increases the risk, it probably does so through

relaxation of the tissues, resulting in lessened resistance to the passage of the instrument. Training in proctology will bring recognition of the danger of instrumental perforation of the rectosigmoid. There should be supervised instruction to attain competence before free use of the instrument is permitted. Such training will emphasize the use of the proctoscope for ordinary examinations; the avoidance of instrumentation by maneuver, the desirability of visual control of all procedures in the upper part of the rectum or the sigmoid with avoidance of force in instrumentation or air dilation, and, finally, the use of exceptional care in manipulations on patients with ulceration of the bowel wall.

The mortality rate, based on 72 cases of instrumental perforations of the sigmoid, was found to be 56 per cent. This is the same figure reported by Burt for rupture of the sigmoid by compressed air. The mortality is increased by delay in closure of the perforation. Crohn and Rosenak found that operation as late as seven hours after perforation was always fatal, and this has been confirmed by the cases subsequently reported and by my experience. The best results are obtained by immediate closure of the hole in the rectosigmoid and removal by suction of any extravasated material. The prognosis is influenced by the amount of fecal contamination of the peritoneal cavity, for peritonitis is the usual cause of death. Early operation on a patient with minimal soiling of the peritoneum offers a reasonable chance for cure.

#### SUMMARY AND CONCLUSIONS

Traumatic perforation of the rectosigmoid occurs most frequently from direct violence. Other causes are ribaldry in "practical jokes," ignorance in self treatment, accidental impalement and sadism or sexual perversion in anal eroticism. Perforation of the bowel by instruments inserted through the anus for diagnostic or therapeutic procedures is fortunately a rare accident. It has been studied in an effort to clarify its causes and prevention. As a result of the study the following conclusions are presented:

1. The healthy rectosigmoid can be perforated by a skilled observer or by a conscious patient without the realization that harm has been done.

2. The hazard is great enough to make supervised training to attain competence necessary before unrestricted use of the sigmoidoscope is permitted. This restriction does not apply to the shorter proctoscope, which is reasonably safe.

3. The greatest safeguard is visual guidance of all instruments passed into the upper part of the rectum or the sigmoid. The greatest danger is from blind instrumentation by maneuver.

4. Particular care should be exercised to avoid instrumental or air pressure in the anesthetized patient or in one with a diseased, ulcerated bowel wall.

5. The mortality rate of instrumental perforation of the rectosigmoid is 56 per cent. Delay of seven hours or more in operative closure is always fatal. The best results are obtained by immediate repair of the perforation.

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## PNEUMATOCELE OCCIPITALIS

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The passage of atmospheric air into the tissues of the cranium and its contents through trauma, infection, tumor growth or congenital defect produces a variety of clinical syndromes. For the purpose of discussion, these disturbances arising from such an invasion may be grouped under the following headings.

1. Emphysema capitis
2. Pneumocephalus internus
3. Pneumatocele frontalis externa, or pneumatocele syncipitalis
4. Pneumatocele supramastoidea
5. Pneumatocele occipitalis

Emphysema capitis represents the diffusion of air between the pericranium and the galea aponeurotica, with or without infiltration of the entire thickness of the scalp. Most commonly it follows operation on the frontal sinus, but it may be recognized as a complication of trauma to the frontal sinus or of operation on the mastoid and must be differentiated from gas-forming infections of the scalp. From a didactic point of view, it must be differentiated as well from the emphysema involving the orbits, facial tissues and neck, noted, for instance, as a sequel of tonsillectomy, of pulmonary injury or of injury to the maxillary antrums. Emphysema capitis is of scant clinical interest, and the infiltration of air may be expected to subside in the majority of cases with expectant treatment.

Pneumocephalus internus (intracranial pneumatocele or arocele, pneumoventricle of the cerebrum, pneumocranium, arocele of the brain, cerebral emphysema) represents the passage of air into the subdural space, the subarachnoid space, the brain tissue or the ventricular system, with the location of the air dependent on anatomic factors at the site of the fistula. The air is commonly forced into the cranial chamber quite mechanically, by a traumatic rupture of the paranasal or mastoid sinuses.<sup>1</sup>

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From the Department of Surgery, Duke Hospital.

1. Dandy, W. E.: Pneumocephalus (Intracranial Pneumatocele or Arocele), Arch. Surg. **12**:948-982 (May) 1926.

Less frequently the condition may develop as the result of tumor growth,<sup>2</sup> and again differentiation must be made from a collection of intracranial air subsequent to the introduction of gas-forming organisms. The symptoms, physical signs, clinical course and treatment of pneumocephalus interna are widely recognized and are adequately discussed by the authors cited.

Pneumatocele frontalis externa, or pneumatocele syncipitalis, represents a more or less encysted collection of air resting between the skull and the pericranium, located over either supraorbital ridge and caused in the majority of cases by trauma. The mechanism of its development demands a break in the continuity of the outer frontal sinus plate without disruption of the pericranium and the forceful, intermittent passage of air through coughing or sneezing into the potential space thus created from which the air cannot be absorbed. It is an extremely rare lesion; it was described in 1891 by von Helly,<sup>3</sup> who reported 17 cases, and has been ignored in the literature since that time. All of the patients in von Helly's series were adults, as might be expected from the late development of the frontal sinus. Etiologic factors were noted, in the order of importance, as trauma with fracture of the outer sinus plate, infection with necrosis of the sinus plate, congenital dehiscence of the anterior sinus wall and the presence of vascular foramens between the frontal sinus and the pericranium, secondarily involved by an infectious process. The diagnosis of pneumatocele syncipitalis was based by von Helly on the notation of one of these etiologic factors, the presence of a smooth, globular tumor above either supraorbital ridge, enlarging during forced expiration and sometimes compressible, giving a tympanitic note on percussion and expelling air on puncture or incision. Therapeutic endeavors in vogue at the time of publication of this paper can scarcely be discussed in the light of modern surgical experience. It is noteworthy that many of von Helly's patients were reported cured by incision and the almost inevitable sequelae of infection, denoting obliteration of the fistulous tract by granulation tissue. In view of the remarkable therapeutic results obtained in the treatment of pneumocephalus internus, it appears obvious that in treatment of the somewhat similar lesion pneumatocele syncipitalis attention should be directed toward surgical obliteration of the fistulous tract.

A clinical differentiation between pneumatocele supramastoidea and pneumatocele occipitalis may be open to the criticism that both pneuma-

2. Campbell, E., and Gottschalk, R. B.: Osteoma of Frontal Sinus and Penetration of Lateral Ventricle with Intermittent Pneumocephalus, *J. A. M. A.* **111**:239-241 (July 16) 1938.

3. von Helly, C.: Ueber die Pneumatocele syncipitalis, *Arch. f. klin. Chir.* **41**:685-704, 1891.

toceles develop from a defect in the pneumatic cells of the mastoid and should be considered minor variations of the same underlying factor. Both types, again, represent encysted air resting between the outer table of the skull and the pericranium, but they may vary markedly in external appearance. Close examination of the condition in the case to be detailed and an analysis of the scattered cases in the modern literature reveal, furthermore, a fundamental etiologic difference that is of profound clinical import.

#### REPORT OF A CASE

S. J., an 18 year old Negro, was admitted to the Duke Hospital on Jan. 20, 1940, with the presenting complaint of a painless swelling of the head of one year's duration.

There was no history of inheritable familial disease. The patient was unmarried. His past health had been excellent; so far as he could recall, there had been only childhood infections and an occasional cold to mar the even course of his physical state. In answer to specific questioning he stated that he had had no serious injuries, particularly injuries to the head, and had had no operations. He recalled no instance of otitic pain or infection but stated that he had been completely deaf in the left ear for as long as he could remember. There was a tendency to dull, bifrontal headache when he was hungry. There was no history of venereal infection. His working, dietary and sleeping habits were exemplary.

One year before admission the patient noticed a small, roughly circular, painless, smooth cystic mass situated in the left posterior parietal region of the skull, closer to the midline than to the ear. He described it as approximately 1 inch (2.5 cm.) in diameter and stated that his attention was first drawn to the mass by his barber. The tumor remained stationary in size and asymptomatic during the following seven months, but during this period, for the first time, he became conscious of an intermittent, low-pitched roaring in his right ear, which he described as "resembling the sound of the ocean."

Five months before admission his barber drew his attention to the fact that the mass was increasing in size, and the observation was made then that tension in the mass was greater on coughing or sneezing. At this time the patient recalled that when he arose in the morning the tumor was soft but that it grew firmer and larger as he became active. Pulsations were felt in the mass four months before admission, and the roaring tinnitus in the right ear occurred more frequently and became more intense and prolonged. In the three months prior to admission the mass tripled in size, according to the patient's observation. Roentgen study of the skull was carried out ten days before admission; the mass was aspirated, air obtained and the patient referred for neurosurgical intervention. The patient's denial of all symptoms referable to a state of increased intracranial pressure was striking, and, indeed, his seeking of medical advice appeared dictated by vanity more than by any other one factor.

General physical study elicited little. The patient was healthy, well developed and normally nourished. In the left posterior parietal region of the cranium there was an oval elevated mass approximately 10 by 5 cm. (fig. 1). The scalp tissue over this mass was unchanged. The tumor was divided into two indistinct lobules, the larger one lying rostrally to a point corresponding to the external auditory canal and the caudal mass extending to within 1 cm. of the transverse sinus plate. The mesial border extended to a point 3 cm. from the midline and its lateral border an equal distance above the ear. The mass was tym-



panitic to percussion, fluctuant and painless. Even with firm pressure no decrease in its size or tension could be demonstrated. When the mouth and nose were closed and forced expiration was attempted (Valsalva's test) the mass increased in size and became tense. No bruit could be heard, and no increase in the tinnitus by means of added pressure could be elicited during the period of observation. A definite pulsation, synchronous with the pulse, was visible and palpable. The margin of the skull about the periphery of the mass appeared depressed and irregular, and in its caudal aspect bony crepitus could be elicited. No alteration in the structure of the skull could be palpated beyond the boundary of the tumor. The external ears and the mastoid regions were normal in appearance. Otoscopic examination showed normal anatomic landmarks. Neurologic examination failed to show any alteration from normal function, with the striking exception of complete loss of hearing and vestibular responses on the left side.

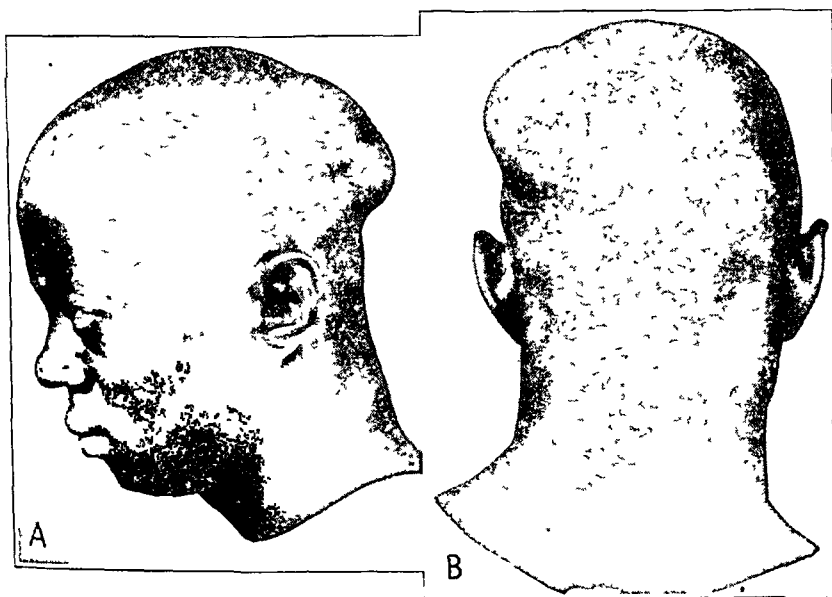


Fig. 1.—Pneumatocele occipitalis. *A*, lateral view; *B*, posterior view.

Lateral and anteroposterior roentgenograms of both mastoid regions showed unusually large cells on the left side, particularly above the antrum. There was no evidence of infection of the mastoid. Immediately above the mastoid region on the left, the diploe and inner table of the skull appeared irregularly eroded. The right mastoid region was normal in all respects.

Lateral stereoscopic and anteroposterior roentgenograms of the skull showed a large collection of air in the left posterior parietal and occipital regions of the cranium. This air appeared to lie between the dura and the inner table of the skull. In the center of this region there were two irregularly rounded defects in the skull, which were surrounded by fine trabeculations. There was a thin line in the posterior temporal region, in the location of the fissura squamosa mastoidea, which communicated with the posterior-superior mastoid cells. This suggested the appearance of a fracture line (fig. 2).

In a personal communication to one of us (T. W. B.), Dr. John D. Camp, of the section on roentgenology of the Mayo Clinic, stated: "The most likely diagnosis, I believe, is a large epidermoid type of tumor of intradiploic origin

involving the superior portion of the temporal bone and the posterior portion of the parietal bone on the affected side. Stereoscopically there appears to be a definite expansion of diploic tissue, and this, together with the irregular appearance of the osseous changes and its sharply demarcated borders, prompts me to make this diagnosis. There is one other very rare and unusual condition which must be considered, and that is an anatomic variation in the development of the mastoid cells, which, because of some unknown anatomic reason, have developed

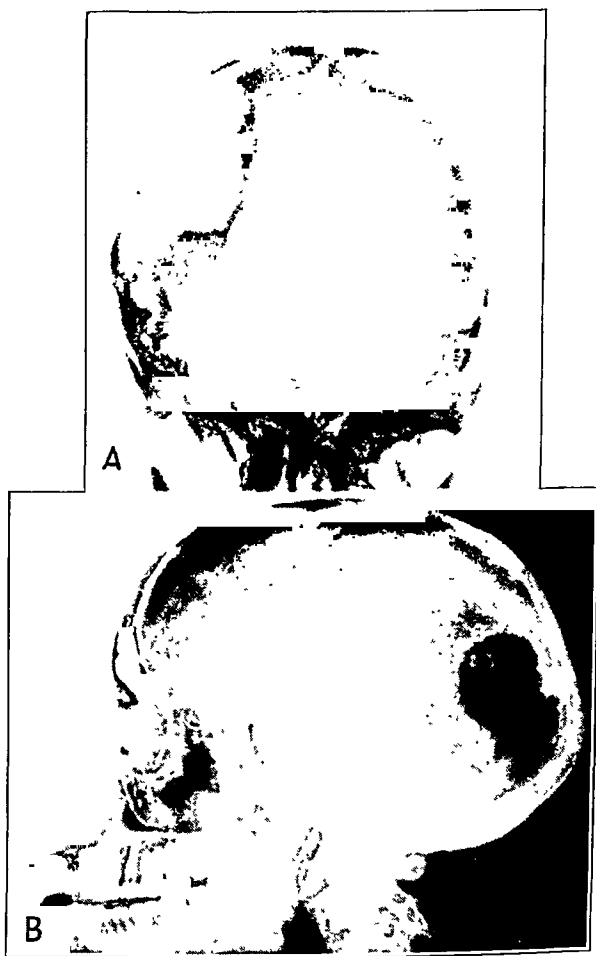


Fig. 2.—*A*, roentgenogram of a pneumatocele occipitalis. *B*, another view.

tremendously and extend up into the parietal bone as indicated. This condition, however, is usually bilateral."

In view of the history and physical findings a preoperative diagnosis was made of "epidermoid tumor with extracranial and extradural pneumatocele."

On January 19 a craniotomy was performed on the left, with exploration of the pneumatocele occipitalis, extracranial and extradural. Avertin with amylene hydrate and ether were used for anesthesia. The operation was performed under bactericidal irradiation. The operative note was as follows:

"This patient was referred to the Duke Hospital by Dr. T. W. Baker, of Charlotte, N. C., and presented a tremendously interesting problem in diagnosis.

Stereoscopic studies of the large defect in the left occipitoparietal region agreed with the findings noted in Charlotte and also by Dr. Camp in Rochester, Minn. However, a small transverse fracture line was noted, lying rather high, near the posterior border of the mastoid antrum. At least, this defect appeared to be of traumatic origin. The patient, also, could markedly expand the defect in the scalp by holding his breath and simulating a forced expiratory movement. The defect in the skull greatly resembled an epidermoid tumor, and the diagnosis rested between that and a pneumatocele, probably of traumatic origin. No attempt was made to aspirate the lesion before operation.

"A crescent-shaped scalp incision was marked out, with its base in the occipital region along the line of the lateral sinus, with its mesial border 1 cm. from the midline just above the inion and with its rostral border about at a point just above the ear. It was noted that with the patient under anesthesia the mass in the scalp protruded markedly, becoming almost one third larger than it had been before anesthesia was induced. This developed in spite of the fact that the anesthesia was markedly smooth. The scalp flap was reflected toward its base caudally; this uncovered a smooth, nonlobulated homogeneous mass apparently covered with somewhat thickened areolar tissue and pericranium. This mass felt cystic and did not resemble tumor tissue. The rough borders of the cranial defect were palpable around its edge. The mass was aspirated and air was obtained, which slightly reduced the size of the mass. A small incision was made over the vertex of the mass. The tissue forming the covering of the mass was about 3 or 4 mm. thick; it was fairly homogeneous and seemed to be ordinary fibrous tissue. When the interior of the mass was opened there was a gush of air under pressure and the entire mass collapsed. This incision was lengthened along the longitudinal diameter of the mass, and it was noticed that the mass was entirely extracranial. The outer cortex of the involved parietal and temporal bone was roughened, and there were many smoother, hollowed-out areas in the bone which resembled those seen about an epidermoid tumor. No tumor, however, was visible. At a point on the parietal mastoid suture line, rather close to the beginning of the lambdoidal suture, there was a circular defect in the cortex of the bone, perhaps 4 mm. in diameter. Slightly rostral to this was a second defect, which was covered with a thin membrane of fibrous tissue. Through the first-noted defect one could see directly into a large extradural defect passing down into the region of the tip of the mastoid. The outer layer of bone was resected, beginning at this aperture, and it was noted that the diploe and inner table had been completely destroyed over most of the areas noted in the roentgenogram. The dura was depressed over this area for a depth of 3 cm., and the entire extradural defect measured perhaps 7 cm. in a coronal line and 9 cm. in a longitudinal line passing diagonally down toward the tip of the mastoid. In several regions there were fine adhesions between the dura and the inner surface of the skull. There were many of these far down toward the mastoid tip. Most of them were delicate, but occasionally one noted rather thick tendinous adhesions. About 2 cm. of the cerebellar dura was visualized, and the transverse sinus and sigmoid sinus passing down toward the jugular foramen could be clearly visualized. Naturally a large expanse of temporal, parietal and occipital dura was opened to inspection. The tendinous adhesions mentioned were carefully dissected free, and at this point two rather remarkable pictures were noticed. In the first place, as the bony dissection was brought laterally toward the mastoid antrum slightly below the region of the parietal mastoid suture line, there was encountered an area in the upper portion of the mastoid which might have been fractured, because it broke away without any effort being made with the rongeur. This represented the position of the supposed fracture

line noticed in the roentgenogram. Far down on the inner surface of the mastoid, passing transversely across the mastoid, cells were open extradurally for a distance of about 2 cm. The margin of the defect was ragged; it was perhaps 3 mm. in width at its greatest portion. The cells were opened, and we immediately entered large, dry irregular cellular spaces. Anteriorly there were visible several small apertures, passing, in all probability, into the mastoid antrum. This defect was filled with warm saline solution, but no definite point of entry for air could be ascertained. These tiny defects were filled with bone wax. A transplant was made from the fascia of the under surface of the temporal muscle over this defect in the mesial surface of the mastoid, and the dura was then tacked up to the transplant with interrupted fine black silk sutures. The only difficult point in this imbrication of tissue rested in bringing the lateral sinus up

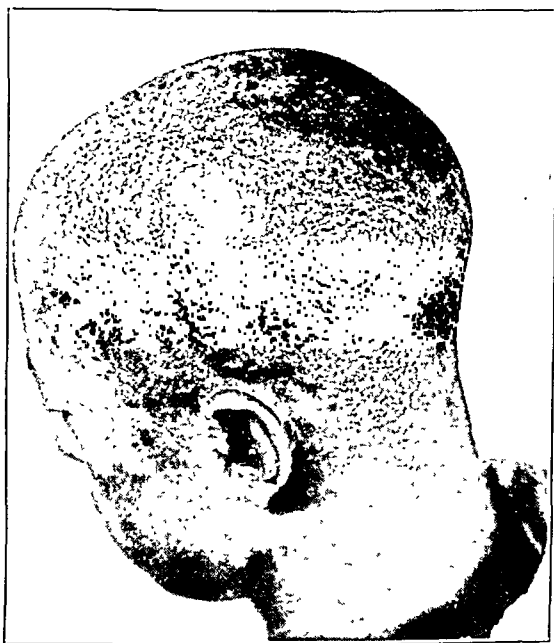


Fig. 3.—Patient after the operation.

to the transplant, which was accomplished by sutures carefully passed through the outer dural surface of the sinus. When this imbrication was completed it appeared to be fairly firm. The entire dural defect was then sutured to the galea about the bony defects made in the exploration by interrupted fine black silk sutures, and this elevation of the dura destroyed perhaps two thirds of the mass of the extradural defect. The tissues comprising the extracranial mass were then brought together with interrupted fine silk sutures, the extradural defect being completely closed from the extracranial tissue. The galea was then closed with interrupted fine silk sutures. The skin was closed with continuous fine silk sutures. The patient's condition remained excellent throughout this procedure."

The patient's postoperative course in the hospital following operation was uneventful, and he was discharged on the eighth postoperative day (fig. 3). No recurrence has been reported to date, although it must be admitted that, possibly in the exuberance following recovery, the patient committed mayhem on a neighbor and has not been seen since, six months after the operative procedure.

## COMMENT

Wernher<sup>4</sup> presented the first discussion of this subject in 1873, under the heading of "pneumatocele cranii, supramastoidea, etc," and described 12 cases, including 1 personal observation. Heineke<sup>5</sup> included 7 cases from Wernher's series and added 2 new cases in a compilation published in the same year. In 1920, Müller<sup>6</sup> reviewed 21 cases and added a personal record. Since that time 5 additional instances of the lesion have been published by Krupsky,<sup>7</sup> a case successively discussed by Laufenstein,<sup>8</sup> by Neuffer<sup>9</sup> and by Neuffer and Singer,<sup>10</sup> and single cases reported by Reverchon and Worms,<sup>11</sup> by Stupka<sup>12</sup> and by Muir.<sup>13</sup> The exact number of cases of pneumatocele occipitalis and pneumatocele supramastoidea in the literature is difficult to ascertain with accuracy, since many of the earlier descriptions are scanty and inadequate as judged by modern standards. The case of Acrel, for instance, appears on review to be simply an instance of emphysema capitis. The cases recorded since 1920, together with the present example, make possible a presentation of the clinical course of pneumatocele occipitalis, a discussion of its pathogenesis and comment concerning surgical treatment.

In this series of approximately 30 cases, pneumatocele occipitalis and pneumatocele supramastoidea were found predominantly in males, and

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4. Wernher, B.: Pneumatocele cranii, supramastoidea, chronische Luftgeschwulst von enormer Grosse durch spontane Dehiscenz der Zellen des Processus mastoideus entstanden, *Deutsche Ztschr. f. Chir.* **3**:381-401, 1873. This review includes the cases of Acrel, Lloyd, Pinet, Wassy, Costes, Vianna, Schmidt, Jarjavay, Balossa and Denonvilliers.

5. Heineke, W. H.: Verletzungen und chirurgische Krankheiten des Kopfes, in Patha, F. J., and Billroth, T.: *Handbuch der allgemeinen und speziellen Chirurgie*, Stuttgart, Ferdinand Enke, 1873, vol. 3, pt. 1A, sect. 1. This article adds the cases of Fleury and Voisin.

6. Müller, W.: Ueber die Pneumatocele cranii, *Beitr. z. klin. Chir.* **120**: 399-411, 1920. This review adds the cases of Kramer, Malapert and Gobilat, Nicod, Jasserand and Carle, Sonnenburg, Strom and Weiss. The cases of Mazzoni, cited by von Helly,<sup>3</sup> and of Brunschvig, cited by Sonnenburg, should be included in this historical summary.

7. Krupsky, A.: Zur Frage der angeborenen Anomalien der Ohrmuscheln, *Ztschr. f. Laryng., Rhin.* **16**:255-258, 1927.

8. Laufenstein, K.: Ueber die Pneumatocele occipitalis, *Beitr. z. klin. Chir.* **145**:524-531, 1929.

9. Neuffer, H.: Beiträge zur Therapie der Pneumatocele occipitalis, *Arch. f. klin. Chir.* **160**:118-121, 1930.

10. Neuffer, H., and Singer, R.: Beiträge zur Therapie der Pneumatocele occipitalis, *Arch. f. klin. Chir.* **190**:299-306, 1937.

11. Reverchon, L., and Worms, G.: Pneumatocèle occipitale spontanée d'origine mastoïdienne, *Dixième Congrès international d'otologie*, Paris, July 1922; abstracted, *Zentralbl. f. Hals-, Nasen- u. Ohrenh.* **3**:431, 1923.

12. Stupka, W.: Ueber die Fehlbindungsnatur der Spontanenstandenen Pneumatocele Supramastoidea, *Acta oto-laryng.* **25**:328-340, 1937.

13. Muir, J. B. G.: Pneumatocele Capitis, *Brit. J. Surg.* **25**:603-607, 1938.

only 1 case has been noted in which the patient was under 12 years of age. This will be discussed in some detail. The pneumatocele occurred spontaneously in 16 of 24 cases; in 5 a significant history of otitis media was obtained, and in 3 the characteristic mass presented itself after trauma to the head. No other details in the preceding histories appeared pertinent.

In the classification presented in the first paragraph of this paper the lesion was divided into two classic types, pneumatocele occipitalis and pneumatocele supramastoidea. Our personal case was an instance of the former type and is duplicated in 7 of the 29 cases studied in the literature. It is best compared to the case reported by Laufenstein, the further clinical course of which was discussed by Neuffer and later by Neuffer and Singer. The patient was a 19 year old boy who noticed two small adjacent tumors in the left posterior parietal area of the cranium eight months before admission to the hospital. The relatively painless swelling became larger, and headache and a feeling of constriction in the right ear could be developed by firm pressure over the mass. Air was obtained by aspiration of the tumor. Normal function was present in both ears. Roentgen study of the skull showed abnormally large air cells extending from the mastoid into the posterior portion of the parietal bone, almost to the midline. Exploration of the air-containing mass through a posterior parietal craniotomy approach disclosed elevation of the pericranium and a "carios" skull, with many communications entering large, dry cells that extended through the skull and laterally toward the mastoid. The dura beneath the altered bone was depressed for a depth of 1.5 cm.; that is, an extradural pneumatocele was present. The gross pathologic picture was similar to that portrayed in our case. Histologic study of these abnormally placed air-containing cells showed only a lining of connective tissue. A fascial fat transplant from the shoulder region was placed in the operative defect in the skull. Wound healing was uneventful.

As was further recorded by Neuffer, a recurrence of the pneumatocele developed one year after the primary operative procedure. The mass was located more or less in the same region of the cranium and presented a similar clinical picture. Antrotomy was carried out by Neuffer as a safer and more efficient means of obliterating the communication between the pneumatic spaces of the mastoid and the air-containing tumor.

Two years later, after a forceful sneeze, the patient experienced a bursting sensation behind the right ear and shortly observed the reappearance of the pneumatocele. The mass expanded rapidly, and the patient complained bitterly of headache and nausea. For the first time, loss of hearing was manifest in the right ear. Pressure on the mass accentuated the symptoms of increased intracranial pressure and exag-

gerated a low-pitched, roaring tinnitus in the right ear. The external and roentgen appearances in this unusual case are suggested in figure 4 and may be compared with those in our own case (fig. 5). The

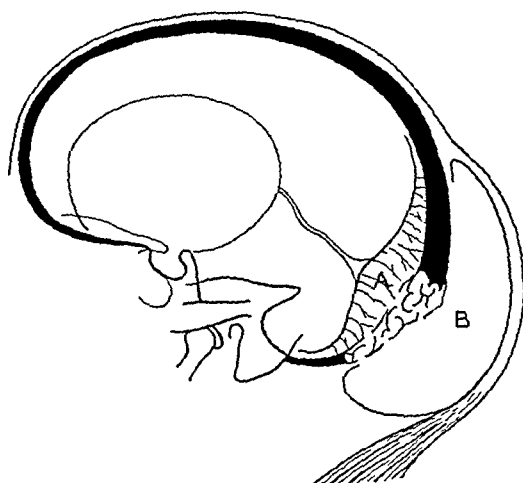


Fig. 4.—Pneumatocele occipitalis, redrawn from Neuffer and Singer.<sup>10</sup> *A*, extradural air. *B*, extracranial air.

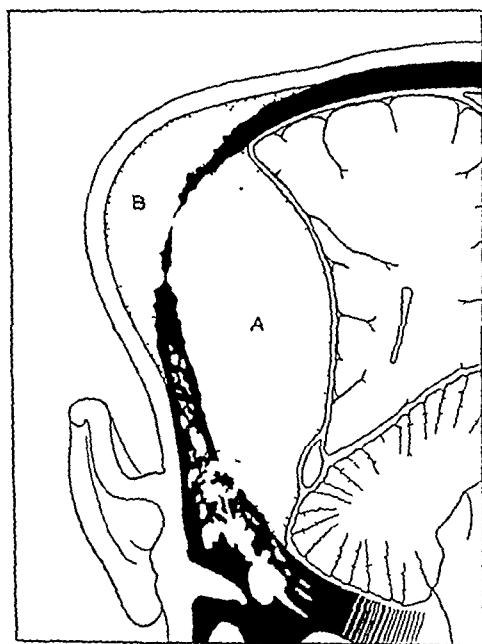


Fig. 5.—Pneumatocele occipitalis. *A*, extradural air. *B*, extracranial air. The cross section was taken approximately through the external auditory canal.

occipital and subnuchal pneumatocele was explored and collapsed through a formal cerebellar approach followed by an atticoantrotomy on the right side (radical operation without resection of the annulus

tympanicus, suggested by Otto Mayer). No evidence of recurrence was reported or could be noted eighteen months later.

In Kramer's<sup>14</sup> case the pneumatocele was described as arising from abnormally pneumatized mastoid cells extending into the occipital bone, without, however, evidence of an extradural extension. Weiss's<sup>15</sup> description of a patient with an occipital pneumatocele strongly suggests an extradural extension, as pressure on the mass caused sudden coma and left hemiplegia. Although the procedure was not carried out in this instance, Weiss advised trephination over the mastoid, rather than direct exposure of the tumor, to obliterate the communication between the pneumatocele and the mastoid cells.

The pathogenesis of this type of pneumatocele rests on an abnormal pneumatization of the posterior parietal and occipital bones of the skull which are in communication with the area of mastoid pneumatization. Such excessive pneumatization or spread of normal mastoid pneumatization was described by Hyrtl<sup>16</sup> as a congenital abnormality. In an examination of 600 skulls, Hyrtl found such an abnormality in 3, in 2 of which the excessive pneumatization was bilateral. The precipitating factor in the production of the pneumatocele may be external trauma, but the condition more often depends on an elevation of intramastoid pressure from sneezing or coughing, with rupture of the outer or the inner bony plate, or both, of the pneumatized area. The pericranium is elevated and the dura depressed by atmospheric air forced into the pseudotumor by a ball-valve mechanism functioning through the pharynx, the eustachian tube, the middle ear, the antrum and the mastoid cells. The dry, carious-appearing, multiloculated involved bone resulting from the excessive pneumatization plus the development of bony spicules arising from fragments of pericranium left in situ forms a picture that has been aptly described by Wernher as a *Reliefkarte eines hohes Alpenlandes*. The external appearance, character and location of the mass, its distention by Valsalva's procedure, its usual lack of compressibility, the frequent occurrence of tinnitus and the intermittent signs of increased intracranial pressure if the inner table of the skull is perforated are all explicable by means of this underlying pathologic change.

Pneumatocele supramastoidea, as is indicated by the term, represents a collection of air between the skull and the pericranium with the tumor presenting above the mastoid, in contrast to pneumatocele occipitalis, with which the external mass presents in the posterior parietal or occipital region of the skull. The initial tumor associated with either

14. Kramer, W.: Zur Lehre von der Pneumatocele cranii occipitalis und deren Behandlung, *Centralbl. f. Chir.* **21**:497-501, 1896.

15. Weiss, M.: Un cas de pneumatocèle du crâne, *Rev. de chir.* **39**:639, 1909.

16. Hyrtl, J.: Pneumatische Hintershauptsknochen, *Wien. med. Wchnschr.* **45**:713, 1860.



type of pneumatocele may spread to involve the entire scalp from the supraorbital ridge to the insertion of the nuchal musculature and even below the occipital protuberance, as was noted in Neuffer's case. Two variations of pneumatocele supramastoidea may exist, the one arising predominantly from a congenital anlage and the second (and more common) arising not only from a dehiscence in the outer wall of the mastoid but from infection or trauma. The latter variation is best illustrated by the cases published by Muller and by Muir.

Muller's case was that of a 50 year old woman who had had chronic otitis media involving the left ear for fifteen years. Eighteen months before admission for surgical treatment, a small painless swelling developed in the superior aspect of the mastoid, following a heavy sneeze. This mass grew slowly to involve the lateral aspect of the skull, corresponding to the extent of the temporal musculature. Air was repeatedly aspirated from the mass. Roentgen study showed a marked periosteal reaction in the outer table of the skull, with pneumatization extending from the mastoid region toward the zygoma. Operation disclosed the characteristic elevation of the pericranium in this region and a change in the outer table and diploe of the skull described by Muller as resembling an osteomyelitic sequestrum. This area of bone was resected and a fascial-fat transplant inserted in the defect. No recurrence was reported.

Muir's case was that of a 24 year old white man who had had a draining ear since infancy. At the age of 4 years a small painless tumor had been noted over the left mastoid region, which changed but little until two years before Muir's observation, when the mass grew rapidly, spreading to involve the entire crown of the scalp. The process of enlargement had been asymptomatic except for periodic attacks of nausea and vomiting. The entire scalp was ballooned out to produce a bizarre, turban-like effect. On gentle palpation the mass was soft but elastic, and on deep palpation sharp spicules of bone could be felt in areas of the skull beneath the tumor. Roentgenograms showed a massive layer of air between the skull and the pericranium, over the entire vault, with many spicules of bone arising from the former attachments of the pericranium to the sutures of the skull. A small amount of air was visualized in the posterior fossa, lying extradurally. Several abnormally large mastoid cells were noted, and in the suprameatal triangle, on the left side, a small aperture in the skull was observed. This was considered to be the original defect in the lateral plate of the mastoid caused by the chronic infection and the precipitating factor in the production of the pneumatocele. In Wernher's case the pneumatocele, apparently of spontaneous origin, presented a similar clinical course. In Wassy's case, reported by Wernher, a similar syndrome was present, following trauma to the skull.

The cases of pneumatocele supramastoidea so far described have in common the appearance of the typical air-containing tumor in the region of the mastoid, from which expansion may occur to involve adjacent areas of the scalp. In these cases there was no evidence of the excessive pneumatization extending from the mastoid into contiguous bones of the skull, which forms a striking feature of the clinical syndrome of pneumatocele occipitalis. In the majority of cases reported, with the exception of that recorded by Muir, intracranial extension of the air is rare, and the escape of air from the cells of the mastoid appears to take place externally. The break in the integrity of the outer wall of the mastoid may occur spontaneously through the agency of a congenital dehiscence, from persistence of the fissura mastoidea squamosa, from infection or from trauma. In the spontaneous type the precipitating factor is again an elevation in intramastoid pressure through coughing or sneezing. The influence of infection and trauma appears obvious, and indeed, as in the case of pneumatocele syncipitalis, infection involving the vascular foramina between the mastoid antrum and the pericranium has been postulated as a factor in the development of pneumatocele supramastoidea.

The second variation with the external characteristics of a pneumatocele supramastoidea is that formed in all probability by the agency of a persistent fissura mastoidea squamosa. Its separation from the more common forms may be of academic interest alone. Krupsky, in a discussion of congenital abnormalities of the ear, has briefly noted the case of a newborn infant with a mass 2 cm. in diameter immediately behind the ear, which increased in size during expiration. Stupka's case was that of a 34 year old man with a number of local malformations, including macrotia, defect of the osseous portion of the external auditory meatus, malformation of the middle ear and asymmetry of the skull and the mandible associated with generalized neurofibromatosis. A small compressible tumor developed behind the left ear ten years before Stupka's study and increased in size with forceful expiration. Roentgen examination showed a normally pneumatized mastoid with a defect in the region of the fissura mastoidea squamosa.

The successful treatment of these three types of pneumatocele related to mastoid pneumatization depends on the obliteration of the communication between the pneumatocele and the mastoid antrum. This principle was recognized in the earliest reports, as was evidenced by therapeutic efforts to close the communication by aspiration and the use of compression bandages, by the injection of sclerosing substances, such as iodine, and indirectly by the observation that incision of the tumor followed by infection of the operative site often prevented recurrence. Modern surgical endeavors have been directed toward what might be termed peripheral resection of the involved bony communications and

closure of the channel by various forms of autogenous grafts. Such procedures are indicated where extradural extension of air is present. The use of bone wax and the further obliteration of the bony defect by transfer of a portion of the temporal muscle as described in the present case appear more efficient procedures than the transplantation of fascial-fat or bone grafts. Neuffer's methods of antrotomy and atticoantrotomy with obliteration of the communication by granulation tissue or development of a fistula in the external canal may be applied to pneumatocele supramastoidea as a primary procedure.

In pneumatocele occipitalis, atticoantrotomy may be used as the second stage in repair of the fistulous communication or may be reserved in case of recurrence after the resection of the pneumatized area by the method described in this paper.

#### SUMMARY

A case of the relatively rare condition known as pneumatocele occipitalis is presented. A brief classification of the syndromes resulting from the passage of atmospheric air into the tissues of the cranium and its contents is discussed, with particular reference to the clinical course, pathogenesis and treatment of pneumatocele occipitalis and pneumatocele supramastoidea.

## SELECTION OF CASES FOR PERITONEOSCOPY

C. ABBOTT BELING, M.D., M.Sc.D.

NEWARK, N. J.

Peritoneoscopy has received more attention during the past year than ever before. Its safety has been well established, and several statistical analyses have been published, the most extensive being Ruddock's,<sup>1</sup> of 900 cases.

Although this information is readily available, peritoneoscopy has not gained widespread recognition as rapidly as its proponents would wish except in a few centers, where it is used frequently with great success. I believe that this is due to the existence of several misconceptions, which in turn arise from the lack of knowledge of the procedure, its indications and its contraindications. The beliefs that the peritoneoscope may be used to visualize anything within the abdomen regardless of its location and that it may be employed to diagnose acute inflammatory conditions are being dispelled to a large extent by the dissemination of information. The most prevalent misconception is that an abdomen must be distended with ascites before the peritoneoscope can be used. It is tied up with the fact that the abdominal cavity must be inflated during use of this instrument and with disregard for the more important fact that the average abdomen undergoes inflation very easily. Until this misconception has been dispelled, many suitable patients will be denied the benefit of peritoneoscopic examination. It is fitting, therefore, to review the previously reported<sup>2</sup> indications and contraindications before proceeding with the discussion of the selection of cases.

### INDICATIONS

Use of the peritoneoscope is indicated with the following conditions:

1. Noninflammatory disease of any of the organs within the greater sac of the peritoneal cavity, excluding the contents and borders of the lesser sac, the pancreas, the kidneys and other retroperitoneal structures, with certain exceptions.

2. A pancreatic growth, particularly one interfering with the continuity of the common bile duct or one suspected of metastasis.

3. A retroperitoneal mass (for determination of the location of an intra-abdominal mass with relation to the peritoneum).

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1. Ruddock, J. C.: Peritoneoscopy, *South. Surgeon* **8**:113-135 (April) 1939.

2. Beling, C. A.: Experiences in Diagnosis with the Peritoneoscope: Indications for Its Use, *J. M. Soc. New Jersey* **36**:602-605 (Oct.) 1939.

4. A suspected neoplasm or anomaly of any of the pelvic organs, including endometriosis.
5. Old chronic inflammatory disease of any of the pelvic organs.
6. Suspected ectopic pregnancy.
7. Splenomegaly or hepatomegaly.
8. Ascites not of cardiac origin.
9. Tuberculous peritonitis.

#### CONTRAINDICATIONS

Use of the peritoneoscope is contraindicated in the presence of:

1. Any acute inflammatory disease of the abdominal cavity.
2. Pneumonia, pulmonary abscess in an advanced stage or disease of the pleura.
3. Advanced pulmonary tuberculosis.
4. Any disease or lesion in the thorax extending into or communicating with the abdomen.
5. A stab wound or bullet wound of the abdomen.
6. Intestinal obstruction or advanced distention of either the small or the large intestine.
7. Acute perforation of any viscus.
8. Heart failure or cardiac decompensation in the absence of ascites, and in the presence of ascites except in certain specially selected cases.
9. Extensive operative scars and adhesions thereto.

#### SELECTION OF CASES

Above everything, the physician must strive to do what is best for his patient. In selecting proper therapy and aids to diagnosis, the choice will rightfully turn toward those procedures which give a maximum amount of information and relief with a minimum amount of risk and discomfort. Different methods will be selected for different conditions, depending on their location, their nature and other factors. Since there are many aids of which the physician may avail himself, it is incumbent on him not to overlook any which may be of importance. The peritoneoscope is one of these and may render unparalleled aid when employed under the proper indications.

Few instruments, if any, are applicable for universal use. The amount of benefit obtained with any instrument, then, will depend first on its mechanical limitations and second on the person who employs it. The success of the peritoneoscopist will depend on his ability to select cases properly, the extent of his personal skill and his experience with the instrument.

In considering any operative procedure on a patient, the risk, discomfort, chances of complications, period of hospitalization and possibility of duplication of procedures must be evaluated. The absence of complications, lack of discomfort and short period of hospitalization following peritoneoscopy have been thoroughly demonstrated and are no longer matters of question. One must not hastily advise peritoneoscopic examination. Each case must be evaluated according to the peculiar problems that it presents. One must strive to formulate an idea of just what can be accomplished by inspection and perhaps by biopsy and to decide whether the information thus obtained would justify use of the instrument.

The fact that a definite diagnosis is frequently made with the peritoneoscope is no excuse for incomplete investigation of a case from other angles.

One would scarcely neglect to listen to a heart with the stethoscope because an electrocardiogram revealed a definite diagnosis not ascertainable with the former instrument. It is the coordination of resources that enables us to make an intelligent decision. Like the electrocardiograph and the roentgen rays, the peritoneoscope gives information which can be obtained in no other way that permits such a high degree of safety.

As the technic of peritoneoscopy has progressed, miracles have been expected of the instrument simply because the requesting physician was not thoroughly familiar with what it can and cannot do. The peritoneoscopist must not fail to realize this fact and to take the trouble to explain the indications. Only thus can he hope to put the instrument to the best and most widespread use, and only thus can he hope not to be called to perform peritoneoscopic examination on a patient with an appendical abscess or an intestinal obstruction. It is even more important that the peritoneoscopist preserve at all costs a critical attitude in selecting cases and that he be not influenced by others to examine patients with the peritoneoscope when he has any doubts as to the existence of contraindications. Too often an instrument instead of its operator is condemned when it has been faultily or injudiciously used.

#### NEOPLASM OF THE STOMACH

Although it is possible to obtain much information from various examinations, including roentgen study, there are still no means of accurately determining the presence of metastases in the liver except exploratory laparotomy and peritoneoscopic study. Without either of these, the decision as to the operability of a patient will always be an estimate of probability and chance, regardless of the skill of the surgeon.

A recent editorial on peritoneoscopy<sup>3</sup> sounded a word of caution, while pointing out that the procedure does have some value. The writer seems to have minimized the value and to have given a rather false conception of the relation between peritoneoscopic examination and exploratory laparotomy. It is necessary to call attention to this because editorial pronouncements tend to mold opinion more than articles themselves.

The statement that "peritoneoscopy will never replace exploratory laparotomy" must be confusing until one knows the writer's definition of exploratory laparotomy. If one accepts the sensible view that exploration is not justified until all other, less severe methods have been employed, it will be apparent that peritoneoscopic examination and exploratory laparotomy do not compete. The former, properly used, is a diagnostic procedure. The latter should be employed for therapy and rarely, if ever, for diagnosis. The frequency with which exploratory laparotomy has been performed is as disturbing as the very name itself, which is ready testimony to the fact that the indications for operation are often not clear.

For peritoneoscopic purposes all suspected gastric neoplasms should be divided into two main groups: (a) those involving actual, impending or inevitable obstruction to the continuity of the organ at the pyloric region or higher and (b) those without obstructive lesions.

It is at once obvious that all in the first group must come to operation for restoration of the continuity of the gastrointestinal tract. Peritoneoscopic examination is contraindicated, because it is an added procedure which cannot give any further information.

The estimation of operability of conditions falling into the second group will be made on the probability of remote and regional metastases, including fixation of the organ. It must be admitted that the amount of posterior fixation of the stomach cannot be accurately determined with the peritoneoscope, though much of the greater and lesser curvatures and of the anterior surface can be seen. Most surgeons will agree that local fixation should not be considered a deterrent to surgical attack in all cases, as the results of such treatment are sometimes gratifying. They will all agree, however, that the presence of metastases in the liver makes operation useless. Ruddock<sup>1</sup> has reported approximately 90 per cent accuracy in recognizing hepatic metastases with the peritoneoscope, and Benedict<sup>4</sup> has demonstrated a high degree of accuracy in determining operability. My own experience is similar. In writing about the great value of peritoneoscopic study in these cases, Allen<sup>5</sup> stated: "So

3. Priestley, J. T.: *Peritoneoscopy*, editorial, *Surgery* 7:615-617 (April) 1940.

4. Benedict, E. B.: *The Value of Peritoneoscopy in Gastroenterology*, *Am. J. Digest. Dis.* 6:512-519 (Oct.) 1939.

5. Allen, A. W.: *Report of Medical Progress: Abdominal Surgery*, *New England J. Med.* 220:290-296 (Feb. 16) 1939.

far, one of its most useful applications has been in carcinoma of the stomach. If there are metastases to the liver or peritoneum exploratory laparotomy should be avoided, since under these circumstances cure is impossible and palliative surgery is rarely worthwhile; also, one third of the patients of this group succumb during their postoperative convalescence."

Every patient with a nonobstructive carcinoma of the stomach should receive the benefit of peritoneoscopic examination.

CASE 1.—A white man aged 48 years was admitted to St. Barnabas' Hospital with weakness, night sweats, loss of weight and progressive exhaustion following exertion, all for three years. Abdominal distress and "hunger pains" had been present for the past year. There were constipation and frequency of urination. The patient had pneumonia in 1924, with suspected pulmonary tuberculosis, for which he was sent to Arizona. A tumor was removed from the rectum in 1934. No local recurrence took place. At examination a freely movable solid mass was felt in the epigastrium. It was not tender. The urine contained a trace of albumin. A blood count showed: red blood cells, 3,360,000 per cubic millimeter; hemoglobin, 47 per cent; white blood cells, 9,600 per cubic millimeter, with polymorphonuclears 64 per cent, lymphocytes 11 per cent and monocytes 3 per cent. Occult blood was repeatedly present in the stools and in the gastric contents. Gastric analysis showed no free acid and a low level of combined acid. Roentgen examination of the stomach showed a very large defect of the greater curvature, about opposite the incisura angularis. Gastrosopic examination (Dr. A. J. V. Klein) revealed the growth in the area described, extending from about 1 inch (2.5 cm.) from the pylorus, involving the body and fundus and consisting of many papillary areas without signs of breaking down. A diagnosis of papillary adenocarcinoma of the stomach was made, and peritoneoscopy was requested to determine the possibility of metastases to the liver.

Peritoneoscopic examination was made Aug. 8, 1938. There were yellowish white metastatic nodules on the anterior surface of the liver, particularly the right lobe.

The clinical diagnosis was confirmed; an additional diagnosis of metastatic carcinoma of the liver was made, and the condition was pronounced inoperable.

With experience it is possible to gain considerable information regarding the consistency, color, appearance and mobility of the anterior portion of the greater and lesser curvatures and the anterior wall. Growths may be seen on the lesser curvature extending onto the lesser omentum, as in case 2, and the degree of invasion of the gastric wall estimated. If the patient swallows a special tube with a light at its end, the stomach can be inflated so that one may see the condition of its walls. In some cases one may be able to transilluminate the organ so as to visualize further the amount of involvement. The coordination of gastrosopic with peritoneoscopic examination will result in even more accurate information.

CASE 2.—A white man aged 47 years had eructation and pains in the lower part of the chest and in the epigastrium for eight months. The pain usually came on about three hours after eating and was eased by milk and soda. There



were no tarry stools, jaundice or clay stools. There had been a loss of 15 pounds (6.8 Kg.) in the past year. The abdomen had increased in size for several months, and he had experienced dull aching pains in both loins. He was admitted to the Newark City Hospital. At examination the abdomen was tense and exhibited shifting dullness and a fluid wave. The abdominal veins seemed more than normally prominent. There was an old McBurney scar. The rectum was normal. The urine contained a trace of albumin and a few leukocytes and erythrocytes. Roentgen examination showed a steerhorn stomach with a marked filling defect extending from its middle third to the pylorus and a large residue after six hours. A clinical diagnosis of carcinoma of the stomach was made, and peritoneoscopic study was requested to determine whether there were metastases to the liver and to ascertain the cause of the ascites.

The examination was made on Feb. 22, 1940. About 2 gallons (8.8 liters) of amber fluid was removed. The liver was finely granular and congested. After the instrument had been introduced up between the posterior surface of the liver and the anterior wall of the stomach, an extensive lobulated or nodular yellowish gray mass was discovered invading the upper portion of the anterior wall, the lesser curvature and the lesser omentum. A diagnosis of carcinoma of the stomach with portal metastases and ascites was made, and the condition was pronounced inoperable.

#### NEOPLASM OF THE COLON OR RECTUM

With the possible exception of tumor of the cecum or of the lower part of the ascending colon, any new growth in or about the colon or rectum threatens the continuity of the intestine and hence must be treated by operation regardless of the presence of metastases elsewhere in the body. The information gained from peritoneoscopic examination will not influence the method of attack.

If there is a lesion of the cecum which, according to the roentgen picture, does not compromise the continuity of the bowel, it may be advantageous to look for metastases in the liver before deciding on operation. The peritoneoscope enables one to do this satisfactorily.

The anterior aspect of the rectum may be inspected from within the pelvis to ascertain the degree of involvement in cases of endometriosis, and the rectum itself may be gently inflated to facilitate the examination.

Except under unusual circumstances, use of the peritoneoscope is not indicated for neoplasm of the colon or rectum.

#### DISEASE OF THE LIVER, BILIARY TRACT OR PANCREAS

Diagnosis of disease of the liver, particularly in the presence of jaundice or ascites, is not easy. The more one examines patients with such disease with the peritoneoscope the less sanguine he becomes regarding the accuracy of clinical diagnosis. Suspected cirrhosis of the liver often turns out to be metastatic carcinoma, and carcinoma of the head of the pancreas with obstruction is often proved to be cirrhosis. When biopsy is added to visual inspection the chances for a correct diagnosis are extremely high. In cases of malignant tumor of the liver and cirrhosis, Ruddock<sup>1</sup> reported clinical errors of 26.5 per cent and 44.1 per cent as

against peritoneoscopic errors of 4.4 per cent and 6.3 per cent respectively. Peritoneoscopic study is therefore the diagnostic method of choice for such conditions.

A satisfactory biopsy specimen can be safely secured from the liver. It is necessary to stop any bleeding by electrocoagulation with the tip of the instrument. A piece may usually be taken from a metastatic nodule with impunity, and there is surprisingly little bleeding after a section of liver parenchyma is removed. When there is advanced cirrhosis a tough capsule may prevent removal of a specimen. The gross appearance of the liver, with reference to color, consistency, condition of the capsule, size and shape, has a great bearing on the diagnosis, and it is important that any one attempting peritoneoscopic removal of a specimen should have adequate knowledge of the gross pathologic aspects of the organ in the living subject. The differentiation between hepatic congestion, biliary obstruction and cirrhosis is important. Sometimes it may be difficult to decide whether a new growth in the liver is primary or secondary, especially in the absence of any demonstrable neoplasm elsewhere in the body. As a rule the primary growth is localized to one portion or lobe of the organ, as in case 3, and may be darker than secondary metastatic nodules. The latter are often umbilicated. In the early stages only one or two metastatic nodules may be found (case 4).

CASE 3.—A white man aged 51 years had indigestion, dark urine and clay stools with diarrhea for four months and increasing jaundice for three months. He was admitted to the Community Hospital. Two weeks prior to admission he had noticed swelling of his ankles, and one week later his abdomen had begun to enlarge. He had lost 13 pounds (6 Kg.) in six months. Examination showed him to be intensely jaundiced; the abdomen was distended with fluid, as was shown by shifting dullness. The edge of the liver was more than 3 fingerbreadths below the costal margin and was slightly tender. There were ankylosis of the right knee and edema of the legs and ankles. The urine contained bile pigment, granular casts and a trace of albumin. The erythrocyte count was 2,820,000 per cubic millimeter, with 63 per cent hemoglobin; the leukocyte count was 11,350 per cubic millimeter, with polymorphonuclears 80 per cent, lymphocytes 12 per cent and monocytes 10 per cent. The direct immediate quantitative van den Bergh reaction was 17.1 mg. The icterus index was 125 to 141. There was also an enlarged gland in the left supraclavicular fossa. A diagnosis of carcinoma of the liver, probably secondary to one in the gastrointestinal tract, was made. Peritoneoscopic examination with removal of a biopsy specimen of the enlarged supraclavicular node was performed on April 18, 1940. About 3,000 cc. of bile-stained fluid was evacuated. The left lobe of the liver was enlarged, and a large portion of the anterior and posterior surfaces, particularly of the latter, was occupied by many firm nodules of varying size, some translucent and many confluent. They were raised from the surface of the liver and extended back as far as could be seen toward the base of the liver. Other nodules were seen on the right lobe, adjoining the falciform ligament. A biopsy specimen was taken. On the basis of the peritoneoscopic appearance a diagnosis of primary carcinoma of the liver or bile ducts was made. This was confirmed by the microscopic sections and subsequently by autopsy. The growth originated in the bile ducts.

The edge of the liver in cases of cirrhosis is prominent and stands out like a smooth band against the lobular pattern on each side of it. A new growth often invades or obliterates the edge. On rare occasions one may encounter a cyst of the liver or an extra lobe. Whenever there is any interference with the portal circulation it is my practice to take infra-red photographs of the abdominal wall to determine the



Infra-red photograph showing the collateral venous circulation in a case of secondary carcinoma of the liver.

extent and nature of the superficial venous circulation. The accompanying illustration depicts the venous pattern in a patient with extensive metastatic carcinoma of the liver with massive ascites.

Peritoneoscopic examination is not indicated for the diagnosis of abscess of the liver. It cannot determine the nature of the abscess, the organism present or the likelihood of extension into the pleural cavity. Penetration into the abscess to recover the contents cannot be considered.

Much information concerning the biliary tract may be obtained with the peritoneoscope, although this instrument should not be employed in the presence of acute inflammatory disease. The gallbladder is usually well visualized and may be palpated with the tip of the instrument. Sometimes it is possible to follow the organ down to the hepato-duodenal ligament and the bed of the liver and to palpate large stones within it. Steady pressure with the instrument may cause partial emptying of the gallbladder.

Obstruction of the cystic duct resulting in a greatly enlarged gallbladder, differentiated peritoneoscopically from suspected cirrhosis, is illustrated by case 4. In the presence of increasing jaundice the visualization of a small contracted gallbladder with various changes in the liver indicative of biliary obstruction will suggest obstruction of the duct, perhaps a carcinoma of the head of the pancreas. Case 5 demonstrated the diagnosis of a carcinoma of the head of the pancreas which was thought to be cirrhosis. The infra-red photographs proved that the so-called caput medusae was in reality a unilateral collateral circulation developed about the old operative scar in the right upper abdominal quadrant as the result of sacrifice of the deep circulation at the time of a previous operation. A large cyst of the pancreas may also be detected, depending on its location and size. Metastases from carcinoma of the pancreas may sometimes be seen in the liver. The peritoneoscope does not lend itself, however, to the diagnosis of other diseases of the pancreas.

CASE 4.—A woman had had pains in the right upper quadrant of the abdomen for the past four to five years. She had consumed from 1 to 3 quarts (0.9 to 2.7 liters) of wine daily, usually before breakfast, and  $\frac{1}{2}$  to 1 pint (0.2 to 0.4 liter) of spirits in the evening for several years. During the past year she had increased her alcoholic intake. She was admitted to the Newark City Hospital because of attacks of colicky pain in the right upper quadrant of the abdomen, with nausea and vomiting. The appendix had been removed seven years previously. She had also had morning nausea for some time.

There were generalized tenderness and rigidity over the entire right side and a portion of the left. The edge of the liver was felt below the right costal margin. The urine and the blood were normal. A galactose tolerance test gave entirely normal results. Roentgenograms of the gastrointestinal tract were normal, but there was a round, dense shadow to the right of the second lumbar vertebra in all films.

A diagnosis of cirrhosis of the liver was made from the aforementioned findings and history. Peritoneoscopic examination was requested for confirmation of the diagnosis.

The examination was made on Feb. 12, 1940. It revealed a much enlarged, tense gallbladder filling the entire right upper abdominal quadrant, from the lateral wall to the falciform ligament. It was grayish and did not empty on pressure. By going around the gallbladder the liver was found to be essentially normal except for a small area of adhesions lateral to the gallbladder. All the other abdominal organs were normal. A diagnosis of hydrops of the gallbladder was made. This was substantiated at operation several days later, when the gallbladder was removed and a stone discovered in the cystic duct.

CASE 5.—A white man aged 46 years had first noticed constipation six months previously. Shortly afterward he passed clay-colored stools. Sharp intermittent pains occurred, radiating to the right scapular region. Small amounts of fried food caused bloating and nausea. He lost 30 pounds (13.6 Kg.) in six months. He was admitted to St. Michael's Hospital, where roentgenograms of the gallbladder and of the gastrointestinal tract were taken and were considered normal. An exploratory laparotomy was performed, however, during which the appendix was removed and adhesions around the gallbladder were found. The pancreas was hard and firm, and a biopsy showed inflammatory tissue. He was discharged with the same complaints. For the four days prior to the present admission (to the Newark City Hospital) he had jaundice.

On examination the abdomen was tense. There was a scar in the right upper quadrant, in the right rectus region. The liver was enlarged to 2 fingerbreadths below the right costal margin. There was tenderness in the right upper quadrant. There was an icteric tinge to the skin. There was collateral venous circulation on the abdominal wall.

The urine was normal except for a 2 plus reaction for albumin and a 3 plus reaction for bile. Occult blood was detected in the feces on one occasion. The bleeding time was two minutes and the clotting time one minute. The value for urea was 11 mg., and that for sugar was 97 mg., per hundred cubic centimeters. The Wassermann reaction was negative. The van den Bergh reaction was immediate and direct. The icteric index was 37 to 100. Analysis of the gastric contents showed hyperacidity, and the material obtained by duodenal drainage was blood tinged.

On the basis of the foregoing data, a diagnosis of obstructive jaundice from a carcinoma of the head of the pancreas was made. Cirrhosis of the liver was also considered. Peritoneoscopic examination was requested to establish the diagnosis.

Because the appearance of the abdominal veins did not seem to be typical of true collateral circulation incident to portal obstruction, infra-red photographs were taken. These demonstrated that collateral veins had developed about the old operative scar and were undoubtedly secondary to interruption of the deep veins at the time of operation and not due to portal obstruction.

When the peritoneoscope was introduced, on March 25, 1940, about 2 quarts (2.2 liters) of yellow-green milky fluid was aspirated. There were numerous yellowish white nodules on the parietal peritoneum, near the liver and along the falciform ligament. The liver was normal except that it was bile stained. Many dense adhesions prevented examination of the gallbladder and part of the right upper abdominal quadrant. All of the other organs were normal in appearance. On the basis of the findings and the character of the chylous fluid, a diagnosis of carcinoma of the head of the pancreas with obstruction of the thoracic duct and metastases was made.

#### THE SPLEEN AND RETROPERITONEAL MASSES

Peritoneoscopic visualization of the normal spleen is difficult because of the anatomic location of this organ. One may state, for practical purposes, that whenever the spleen is seen it is enlarged. Various types of cysts may be recognized. A diffusely enlarged spleen can be studied from the standpoint of color, consistency and surface appearance. Infarcts and neoplasms may thus be seen. Not infrequently it is important to decide whether a mass in the left upper abdominal quadrant

is the spleen or a kidney, and peritoneoscopy enables one to do this satisfactorily in the majority of cases, although one may be fooled by an unusual condition, as in case 6.

CASE 6.—A white woman aged 58 years was admitted to St. Barnabas' Hospital with a history of constipation, belching and general dyspepsia for several years. Pain in the left side had been present for several months, accompanied with loss of appetite, loss of weight, weakness and night sweats. Her condition had been especially bad for several weeks, and four days previously she had had a chill followed by a fever, which had persisted. There were no urinary symptoms. There was a history of several attacks of malaria years ago in the South.

In the upper left abdominal quadrant there was a mass which extended at least 3 cm. below the left costal margin, was tender and seemed to have the notch and the conformation of a spleen. Malaria, malignant tumor of the gastrointestinal tract and several other conditions were suspected. The urine was normal except for a trace of albumin. There was leukopenia, the white blood cell count being 5,000 per cubic millimeter, but the differential count was normal. There was slight achromia of the red cells, and the value for hemoglobin was 71 per cent. Peritoneoscopic examination was performed to establish the diagnosis.

The liver, gallbladder, stomach, intestines, omentum and peritoneum were normal. A mass in the left upper quadrant of the abdomen was visualized with ease and appeared to be the spleen. The edge was sharp and well defined and presented a notchlike indentation. The anterior and posterior surfaces and the medial border were inspected. The color was abnormally grayish, and there were but few reddish areas. The organ was firm and tender on pressure. A diagnosis of splenomegaly was made.

Splenectomy was attempted because of the aforementioned findings. The operator reported: "When the abdomen was opened, the spleen was found greatly enlarged, nodular and firmly adherent to the left kidney, diaphragm and small intestine. Its surface varied in color, but no area of infection was made out." No definite pedicle could be found, and the mass was separated from the kidney. It was then suspected that it was not the spleen. Sections proved it to be a large hypernephroma which had penetrated through the peritoneum and had assumed the shape of the spleen.

The diagnosis of a mass felt through the abdominal wall is surrounded with many uncertainties, particularly when it comes to making a decision as to the precise location. Sometimes it is important to determine the position more accurately so that the growth can be attacked surgically from the most advantageous approach. By use of the peritoneoscope one can often accomplish this. When the mass is strictly retroperitoneal it cannot be moved. It is seen only through the mesentery of the bowel, if at all, and biopsy specimens cannot be taken with safety. Its relation to the intraperitoneal organs may be extremely important if the retroperitoneal mass happens to extend up into the mesentery of the small bowel or is movable. In case 6 there was revealed a rare combination of an intraperitoneal mass arising from a retroperitoneal mass, and the condition was for that reason most confusing. In case 7 such a differential diagnosis was made by peritoneoscopic examination, and the influence of this diagnosis on the surgical attack is demonstrated.

CASE 7.—A white man aged 55 years was admitted to St. Barnabas' Hospital. About four months previously the patient had first noticed that he was losing weight. Since then he had lost about 20 pounds (9 Kg.). His appetite had been extremely poor, and for several weeks he had complained of pains in the upper left abdominal quadrant. Aside from the regular moderate use of alcohol his history was one of good health.

The urine was normal except for a faint trace of albumin. The red blood cell count was 4,000,000 per cubic millimeter, with 65 per cent hemoglobin. The white blood cell count was 8,200 per cubic millimeter, with polymorphonuclears 79 per cent, eosinophils 2 per cent, basophils 1 per cent, lymphocytes 14 per cent and monocytes 4 per cent. Cystoscopic study Oct. 5, 1938, with retrograde pyelograms, showed both kidneys filled normally. The left kidney was placed low, being pushed down by a mass on the left side. Peritoneoscopic examination was requested to determine whether the mass was intraperitoneal or retroperitoneal and to decide on the proper operative approach.

This examination was made on October 12. The omentum was teased out of the left upper quadrant to visualize the contents. There was a narrowing of the space between the parietal peritoneum and the viscera, due to a firm, immovable mass behind the peritoneum. It was not tender, and nothing but intestine and mesentery could be seen over it. There was no invasion of the mesentery. The remaining abdominal organs were normal. A diagnosis of retroperitoneal mass was made, and a posterior operative approach was advised.

Operation, performed about one week later through the posterior route, proved the advice to be correct; the mass was a retroperitoneal sarcoma.

The peritoneoscope should be used to differentiate between an intraperitoneal and a retroperitoneal mass when no definite diagnosis can be made by other means, exclusive of surgical intervention.

#### NEOPLASM OF A PELVIC ORGAN

The history, together with bimanual examination, is sufficient for an accurate diagnosis in a large proportion of cases of suspected pelvic growth. For example, it is not too difficult to determine the presence of a uterine fibromyoma or of an ovarian cyst which is attached on a long pedicle and floats around within the peritoneal cavity. In many cases, however, palpation of the mass in the pelvis gives inconclusive results, and the diagnosis is a matter of conjecture.

Peritoneoscopic visualization is indicated for the establishment of a correct diagnosis in all obscure cases of suspected pelvic growth. In his report of medical progress, Meigs<sup>6</sup> emphasized the importance of such visualization in the differentiation of ovarian tumor and uterine fibroid, for example, and mentioned its application for a number of other pelvic investigations. He has again stressed its use whenever pelvic examination is not conclusive.<sup>7</sup> A small tumor of the ovary not amenable to any other means of diagnosis can be identified by peritoneoscopic examination and biopsy, as in case 8.

6. Meigs, J. V.: Report of Medical Progress: Gynecology, New England J. Med. 220: 242-243 (Feb. 9) 1939.

7. Meigs, J. V.: Cancer of the Ovary, Surg., Gynec. & Obst. 71:44-53 (July) 1940.

CASE 8.—A white woman aged 64 was admitted to St. Barnabas' Hospital. There had been gradual enlargement of the abdomen for several months. Heart-burn occurred after meals. Weakness and pains in the back had been present for one month; there were pains in the upper part of the chest and in the back and difficulty in lifting the left arm. A nonproductive cough had been present for two weeks. There was polyuria, and the patient had lost 12 pounds (5.4 Kg.) in one month.

Examination showed essentially normal conditions except for symmetric moderate enlargement of the abdomen, which was obese. Slight tenderness was elicited on pressure in the left fornix, but otherwise the pelvic examination revealed no abnormality. There was no history of bleeding.

There were normal urine and a normal blood count. Roentgen examination of the lungs showed a normal bony framework but greatly increased hilar shadows. The right side of the diaphragm was elevated, and the pleura was thickened. There was evidence of hilar pathologic change on both sides, probably due to some glandular enlargement which might be secondary to a malignant tumor or to some systemic glandular disease.

On the basis of the aforementioned observations, a diagnosis of malignant tumor of undetermined location was made, and peritoneoscopic examination was requested to establish the true diagnosis.

On June 17, 1939 this examination was performed. Approximately 2 gallons (8.8 liters) of yellow chylous fluid was removed by suction. The contents of the entire abdomen were normal, and nothing was discovered until the left side of the pelvis was inspected. The left ovary was slightly enlarged, grayish and nodular. Near it there were three clusters of yellowish gray nodules on the parietal peritoneum of the pelvis, just to the left of the bladder. A small but prominent blood vessel was seen entering the largest cluster of nodules, which was near the entrance of the round ligament through the parietal peritoneum of the abdominal wall. A diagnosis of carcinoma of the left ovary was made and confirmed by microscopic examination of the biopsy specimen.

On the basis of the observations, the pathologic process in the hilar regions was considered to be enlarged lymph glands full of metastases obstructing the main lymph ducts, which accounted for the existence of chylous fluid in the abdomen.

The condition was obviously inoperable, and operation was not recommended.

No diagnostic method can detect papillary cystadenoma of the ovary with such consistent accuracy as can peritoneoscopic study. On rare occasions one may find a papillary adenoma of the ovary which has remained local, and operative removal may result in recovery. The absence of metastases cannot be determined without doubt except by visual examination, which means use of the peritoneoscope. Case 9 illustrates this point.

CASE 9.—A white woman aged 52 was admitted to St. Barnabas' Hospital.

In 1920 the patient had had an attack of encephalitis, and since then she had had increasing tremors of the extremities, a masklike facies and scanning speech. Salpingectomy had been done twelve years previously. Approximately two years previously she had strained herself while lifting, and a ventral hernia had developed. For the past several months her abdomen had gradually increased in size, and the hernia had bothered her very much, so that she had had to wear a rigid support around her abdomen. Operation for the hernia had been advised



and refused. About four months previously her ankles had commenced to swell. On admission her abdomen was greatly distended, so that she had some difficulty in breathing.

Because of her generalized spasticity and tremors she was unable to help herself. She was emaciated, but her heart and lungs were in satisfactory condition. The abdomen was greatly distended and exhibited shifting dullness. There was some tenderness on pelvic examination, the results of which were not satisfactory because of the intense ascites.

The blood counts and the urine were normal. The possibility of ovarian carcinoma was considered likely, and peritoneoscopic examination was advised to determine the nature and extent of any growth which might be present.

On Oct. 7, 1938 the peritoneoscope was inserted, and about 2 gallons (8.8 liters) of clear yellow fluid was evacuated. Several loops of small bowel were lightly attached to a large, luxuriant, soft, yellowish white papillomatous growth, which filled the pelvis. The major portion of the growth was in the left side. Several pieces were removed with biopsy forceps. The liver, the parietal peritoneum and both the large and the small bowel were entirely free from metastases. A diagnosis of operable papillary cystadenoma of the ovary was made, and operation was advised.

On October 18 operation was performed and the mass, as described, removed successfully from the pelvis. It arose from the left ovary. A cyst of the right ovary was also removed. No implantations were discovered. Microscopic sections of the biopsy specimen obtained with the peritoneoscope and of the specimens taken at operation confirmed the diagnosis of papillary cystadenoma of the ovary.

Recovery from the operation was uneventful; the abdomen did not refill with fluid, and the wound healed well. The patient was up and about and ready to go home when she contracted lobar pneumonia, to which she succumbed.

Endometriosis can be detected by peritoneoscopic examination, and in cases of advanced involvement the procedure may determine the amount of involvement of the anterior wall of the rectum and disclose the extent of endometrial tissue in the pelvis. Biopsy, of course, confirms the diagnosis.

A large ovarian cyst is readily detected by routine physical examination. The size necessitates operation, and therefore use of the peritoneoscope is contraindicated. A patient with severe cardiac disease or a patient of advanced age with little strength, however, may be in such a condition as to preclude operation. Benedict<sup>8</sup> visualized such a cyst in an elderly patient and succeeded in evacuating it under direct vision. This accomplishment should be remembered for further application as the occasion arises.

The rare occurrence of such a condition as that in case 9 is no indication for the performance of exploratory laparotomy on every patient with suspected papillary cystadenoma of the ovary with the hope that the growth may prove to be operable. The mortality, complications, discomfort and period of hospitalization which follow laparotomy are

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<sup>8</sup> Benedict, E. B.: Peritoneoscopy, *New England J. Med.* **218**:713-719 (April 28) 1938.



Tuberculous salpingitis is easily recognized, and biopsy settles the diagnosis. Hydrosalpinx and other tubo-ovarian masses of inflammatory causation can be detected, as well as the extent of their adhesion to other structures. Obviously it is impossible to penetrate deep into the pouch of Douglas in the presence of dense adhesions.

Peritoneoscopic examination has been recommended and employed to determine the occurrence of ovulation by inspection and to detect the absence of one or more ovaries. An anomaly or abnormality of the uterus, such as bicornuate uterus or aplasia, can be seen. The procedure has also been suggested for the determination of the true sex of hermaphrodites, and it would seem wise to examine all such persons with the peritoneoscope before considering plastic reconstruction of the external genitalia.

The diagnosis of ectopic pregnancy is not always easy, as any one who has practiced gynecology and obstetrics will testify. In 1937, Hope<sup>9</sup> wrote the first discussion of the use of the peritoneoscope for the differential diagnosis of this condition. Ruddock's<sup>1</sup> analysis of 58 cases of suspected ectopic pregnancy investigated with the peritoneoscope revealed a clinical accuracy of 50 per cent and a peritoneoscopic accuracy of 100 per cent. Seventeen of the 29 conditions clinically misdiagnosed were proved to be intrauterine pregnancies; one fourth of these were associated with inflammatory disease. Seven others were uncomplicated inflammatory conditions. Miller's<sup>10</sup> review (1940) of 137 cases of ectopic pregnancy at the Touro Infirmary, New Orleans, from 1924 to 1936 revealed a correct diagnosis in 47.2 per cent of cases and the fact that the condition was highly considered in an additional 23.5 per cent. Statistics speak well for the peritoneoscope, but the use of the instrument in certain centers for this purpose has not met with widespread approval. With the recent methods of detecting hidden hemorrhage by the hematocrit, the falling drop specific gravity of the blood and the plasma proteins, it would seem that the percentage of clinical accuracy must increase in diagnosing ectopic gestation when active hemorrhage occurs. Peritoneoscopy, however, should not be overlooked whenever the element of doubt assumes any great proportion.

#### TUBERCULOUS PERITONITIS

In the past the diagnosis and treatment of tuberculous peritonitis have been unsatisfactory. The diagnosis was usually made by performing an exploratory laparotomy; at the time of this operation atmospheric air was admitted and the interior of the abdominal cavity

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9. Hope, R. B.: The Differential Diagnosis of Ectopic Gestation by Peritoneoscopy, *Surg, Gynec. & Obst.* **64**:229-234 (Feb.) 1937.

10. Miller, H. E.: Ectopic Pregnancy: Review of One Hundred and Thirty-Seven Cases, *Am. J. Surg.* **48**:47-56 (April) 1940.

thoroughly handled. A number of patients seemed to be improved after laparotomy without further manipulation. This suggested the idea that the introduction of air into the peritoneal cavity might be responsible for the result. Still other patients were apparently helped by the administration of an anesthetic without operation, although in their cases the diagnosis was not always certain.

Today it is no longer necessary or advisable to subject these patients to the hazards of laparotomy. With the peritoneoscope the peritoneal cavity can be thoroughly inspected; a biopsy specimen can be taken, and a definite diagnosis of tuberculous peritonitis can be made. This was formerly impossible without operation. Furthermore, the peritoneoscope has the added advantage of being a means by which one can introduce air into the abdominal cavity under tension.

Use of the peritoneoscope is therefore the method of choice for the diagnosis and treatment of tuberculous peritonitis. Case 11 also demonstrates the use of simple pneumoperitoneum at later dates.

CASE 11.—A Negress aged 25 was admitted to the Newark City Hospital on Oct. 7, 1938. One week before admission she first noticed enlargement of the abdomen, soreness under the ribs and a sensation as though she was "burning up," especially at night. Diarrhea had been present for the past week, without passage of blood. She had vomited once, six days previously. There was no history of cough or hemoptysis. She had been treated for "gastritis" four months previously. She had had nocturia (three to four times) during the past week. Examination showed a considerably distended abdomen, with shifting dullness. There was no tenderness, and no masses were palpated. The consistency was not definitely doughy. The sputum was repeatedly normal. The urine contained a trace of albumin. The blood count showed moderate secondary anemia. A clinical diagnosis of tuberculous peritonitis was made, and peritoneoscopic examination was requested to verify it.

The peritoneoscope was inserted on Nov. 11, 1938. Four quarts (4.4 liters) of straw-colored fluid was removed. Tubercles and numerous whitish infiltrated areas were seen on the small bowel. Many whitish flakes were seen here and there. The abdomen was inflated with air and the trocar withdrawn. The diagnosis of tuberculous peritonitis was confirmed.

Within forty-eight hours the temperature, which had been elevated for some time, dropped to normal and continued at that level until her discharge. She remained well, without any symptoms or enlargement of the abdomen, for one year and was readmitted to the hospital during the spring of 1940. Pneumoperitoneum was again produced, with the same dramatic result.

#### ABDOMINAL ASCITES

The causes of ascites are many, and their determination is often difficult. Abdominal paracentesis usually does not solve the problem. The peritoneoscopist soon realizes that unexpected things are found on visual inspection and that clinical accuracy in diagnosing ascites is not high.

It has long been the custom to perform paracentesis on patients with fluid in the abdominal cavity. This was done to relieve the symptoms due to the distention and to obtain some of the fluid with the hope that chemical examination and smears would afford a diagnosis. Introduction of the peritoneoscope entails a similar procedure with no further discomfort; enables more complete removal of fluid, with the possibility of obtaining specimens from different levels within the abdominal cavity, and affords the great advantage of visual inspection and the equipment for obtaining a biopsy specimen if one can be secured. Although these features are evident and indisputable, the peritoneoscopist is frequently amazed that paracentesis has been resorted to before he was called. This cannot be defended as a necessary procedure, because use of the peritoneoscope accomplishes the same purpose with as much ease and with more information. Paracentesis is no more justified as a primary diagnostic and therapeutic procedure in such cases than is a peritoneoscopic procedure in a case of impending pyloric obstruction. After a correct diagnosis made with the aid of the peritoneoscope it is permissible to resort to the trocar for periodic evacuation of the fluid.

#### COMMENT

I do not believe that the slowness with which the aforementioned principles have been accepted is due to a refusal on the part of my colleagues to subscribe to them, as the facts seem to be incontrovertible and should appeal to all conservative thinkers. The use of the peritoneoscope will surely find wide approval as its advantages become known. It is strongly urged, therefore, that all physicians familiarize themselves with the instrument, so that it may take its rightful place in the diagnostic and therapeutic armamentarium, to be employed whenever the proper opportunity presents.

# TRAUMATIC PACHYMENINGITIS INTERNA AND SUBDURAL ABSCESS

WITH SPECIAL REFERENCE TO PATHOGENESIS AND PATHOLOGY

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AND

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LOS ANGELES

Subdural abscess stands preeminent as the most neglected and most misunderstood of all intracranial suppurative lesions. It is not mentioned in any of the general textbooks on pathology, nor is it considered specifically in the majority of monographs or texts concerned with the pathology of the nervous system. Contemporary otologic or rhinologic literature has little to say about subdural abscess other than to give it occasional passing mention as "abscess" or more rarely as "subdural abscess." It is often mistaken for septic meningitis, the observer not distinguishing the pus in the subdural (extra-arachnoid) space from that beneath the arachnoid. It is to this neglected lesion, particularly as it applies to craniocerebral injuries, that attention is particularly directed in this paper. It is the object of this study to establish subdural abscess as a distinctive suppurative lesion which may complicate craniocerebral trauma, to present certain facts regarding its evolution and character and to report 5 cases which have come to our attention.

## REVIEW OF THE LITERATURE

The literature dealing with traumatic subdural abscess is very scant, and what we have been able to find has been stumbled on in general reading, since but one definite article dealing with the specific lesion under this title has been found in any of the various medical indexes. As will be shown, this title proved to be largely misleading. Subdural abscess is not mentioned or described by that name in any of the French or German treatises on injuries of the skull or brain.

It is evident, however, from the reference to the lesion by Guthrie<sup>1</sup> that traumatic subdural abscess is by no means a modern lesion. Writing almost a century ago, he stated:

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1. Guthrie, G. J.: *On Injuries of the Head Affecting the Brain*, London, J. Churchill, 1847.

All foreign bodies should be removed from under the dura; the wound in the dura should if necessary be enlarged. When matter is circumscribed under the dura there is some hope. The records of surgery supply many cases in which incision of the dura to give exit to pus or blood has been done or might have been done with advantage; incision of the dura is more commonly done in France than in England.

While it is not clear from this short statement that Guthrie was able to distinguish between pus in the subdural space and superficial cerebral abscesses which might be opened incidentally by an exploring bistoury, the possibility that he did so distinguish them must be admitted.

As has been mentioned, the solitary reference to traumatic subdural abscess found in the "Index-Catalogue of the Library of the Surgeon General's Office" was misleading, in that it included all *intradural* abscesses, those in the brain having the lion's share of attention. Nevertheless, in a study under this title, Stokes<sup>2</sup> described a lesion which may well be a true subdural abscess. He described the situation in the case (case 1) of a man aged 26 who was struck on the left temporal region with the handle of a reaping hook during an altercation. He recovered from the injury but complained of residual headaches. Some weeks later he became unconscious and it was decided to explore the region of the initial trauma. A trephine opening was made in the region of the scar, but only clear straw-colored fluid was recovered from the subdural space. He died the next day. Stokes<sup>2</sup> stated: "At the autopsy, an abscess, containing fully two and a half or three ounces of cream-coloured pus, and lying directly under the dura mater was found immediately behind the situation where I trephined." This may have been a true traumatic subdural abscess, but it seems unusual that so large a subdural collection of pus should be so circumscribed.

No doubt isolated instances of this lesion appearing in the medical literature have escaped our attention, in spite of our extensive search for such cases. Probably typical of the group is the case described by Cairns.<sup>3</sup> A man of 46 years was knocked down by an automobile, sustaining a comminuted fracture of the frontal region. Death occurred sixteen days later. At autopsy a small subdural abscess was associated with a laceration of the dura over the cribriform plate. A small abscess in the right frontal lobe was also found. The subdural suppuration was too small to be of clinical significance.

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2. Stokes, W.: On Traumatic Subdural Abscess of the Brain, in *Selected Papers on Operative and Clinical Surgery*, edited by W. Taylor, London, Baillière, Tindall & Cox, 1902.

3. Cairns, H.: Injuries of the Frontal and Ethmoidal Sinuses with Special Reference to Cerebrospinal Rhinorrhea and Aeroceles, *J. Laryng. & Otol.* **52**:589 (Sept.) 1937.

## INFLAMMATORY LESIONS OF THE DURA MATER

Since the dura mater is a connective tissue membrane with an abundant blood supply, primary infections do not localize within its tissues. Any suppurative infection affecting it must therefore arise in some adjacent focus. When its external surface becomes inflamed by extension from suppuration in the middle ear, mastoid or frontal sinus, the membrane reacts much the same as any similar connective tissue structure, with variable degrees of congestion, exudation and formation of granulation tissue. In the presence of histolytic organisms or a mixed infection with anaerobes as well as aerobes, local erosion of the dura may take place, with secondary involvement of the subdural space, of the leptomeninges and at times of the brain itself. When the inflammatory reaction is unaccompanied with any gross accumulation of purulent exudate, the lesion is properly designated as pachymeningitis externa or pachymeningitis interna, as the case may be. When the dura is locally penetrated by the inflammatory process, the designation of pachymeningitis penetrans has been proposed to indicate the focal external and internal lesions, together with the fistula which connects them.<sup>4</sup>

When the accumulation of purulent exudate is sufficiently large to be visible to the naked eye, the lesion is designated as an extradural or a subdural abscess. The former rarely assumes clinical importance. Subdural abscess, on the other hand, is a serious and usually fatal lesion. Its presence unfortunately is seldom recognized during life.

## POST-TRAUMATIC DURAL INFLAMMATORY LESIONS

One probable reason for the relative rarity of dural inflammatory lesions after trauma is the proper antiseptic attention which is now usually given to injuries of the scalp and skull. A century and a half ago, when Sir Percival Pott described his "puffy tumor" of the scalp, a lesion which followed local injury, the accumulation of pus beneath the skull and external to the dura as a consequence of focal osteomyelitis was apparently not of unusual occurrence. Even today, osteomyelitis of the skull following trauma is not too uncommon, and in such a condition the presence of pus in contact with the external layer of the dura

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4. This situation is a familiar one to those whose impressions of the stages leading to the formation of a typical otogenous abscess of the temporal lobe are gained from textbook descriptions. In the experience of one of us (Courville) it is rather exceptional, even at autopsy, to find the complete lesion in such cases (Courville, C. B., and Nielsen, J. M.: *The Pathogenesis of Otogenous Abscess of the Temporal Lobe*, West. J. Surg. **43**:680 [Dec.] 1935). It is a more common observation in cases of otogenous abscess of the cerebellum (Courville, C. B., and Nielsen, J. M.: *The Pathogenesis of Otogenous Cerebellar Abscess*, California & West. Med. **47**:29 [July] 1937).



is to be assumed.<sup>5</sup> When drainage is at all adequate there is little danger of extension through the dura either directly or indirectly.

Traumatic subdural abscess must be a relatively rare lesion. We have found in the records of the Cajal Laboratory only 5 cases in a series of 430 instances of fatal injury to the skull and brain. A study of these 5 cases of traumatic abscess and of a number of cases of subdural abscess due to other causes suggests several possible pathways of invasion, which serve as a basis for the following classification.

*Type 1.*—Subdural abscess due to direct implantation of infectious material into the subdural space through a compound, comminuted fracture of the skull.

*Type 2.*—Subdural abscess due to extension of infection from traumatic cellulitis of the scalp.

*Type 3.*—Subdural abscess consequent to traumatic osteomyelitis of the skull.

*Type 4.*—Pachymeningitis interna, or local subdural abscess complicating intracranial aerocele.

*Type 5.*—Subdural abscess consequent to traumatic frontal sinusitis.

*Type 6.*—Subdural abscess due to traumatic otitis media and mastoiditis.

*Type 7.*—Subdural abscess due to rupture into the subdural space of a traumatic abscess of the brain.

While examples of all of these types have not been studied by us, the possibility of extension by various routes from different types of traumatic lesions has been considered possible in the light of the knowledge of subdural abscess viewed in its entirety.

*Type 1.*—The concept of subdural abscess due to direct implantation of infectious material in the subdural space is based only on a theoretic possibility, no definite examples having been studied by us. It would most probably occur after knife, bayonet or sword wounds. It would be less apt to develop directly after gunshot or shell wounds, because the concomitant wounds of the brain or of the meninges would result in the patient's death before a subdural abscess could develop. In the American Civil War, when saber wounds of the head were not unusual in the course of cavalry encounters, "pus beneath the dura" was mentioned among other intracranial lesions,<sup>6</sup> although septic meningitis and

5. Adelstein, L. J., and Courville, C. B.: Traumatic Osteomyelitis of the Cranial Vault, with Particular Reference to Pathogenesis and Treatment, *Arch. Surg.* 26:539 (April) 1933.

6. Otis, G. A., in Barnes, J. K.: Medical and Surgical History of the War of the Rebellion (1861-1865), Washington, D. C., Government Printing Office, 1870, pt. 1, vol. 2. Courville, C. B., and Platner, C. D.: The Etiology of Traumatic Meningitis: A Survey of Ninety Cases Verified at Autopsy, *Bull. Los Angeles Neurol. Soc.* 3:150 (Dec.) 1938.

not subdural abscess was possibly the lesion in question. None of the articles dealing with wounds of the head during the World War mention the lesion.

*Type 2.*—Subdural abscess secondary to traumatic cellulitis of the scalp must also be a very rare lesion; in none of the reported cases of traumatic cellulitis which we have chanced to observe was such cellulitis followed by this lesion. However, when one considers the possibility of extension of infection of the scalp through the emissary veins into the superior longitudinal sinus and thence into the subdural space by way of the superior cerebral veins, this possibility must be admitted. The condition in case 1 of our series may have been so caused, although an osteomyelitis of the skull intervened between the cellulitis and the pachymeningitis interna.

*Type 3.*—Subdural abscess consequent to traumatic osteomyelitis of the skull is probably not as rare as the lack of available literature would seem to indicate. The condition in the first case in our series seems to be a typical example. The infection extends to the subdural space by way of venous connections rather than directly through the dura, for even widespread extradural suppuration has not been known to cause focal necrosis and direct extension into the subdural space. In our case no such fistula was found.

*Type 4.*—Pachymeningitis interna, or local subdural abscess complicating intracranial aerocele, is not often of clinical interest, the lesion constituting only one link in the chain which composes this pathologic complex. As a rule, the subdural inflammation is limited to the vicinity of the fistula, where the air passes through the laceration in the dura, usually behind the frontal sinus or over the ethmoid cells. When the local wall of protection breaks down, the infection extends in the regional subdural space to form a subdural abscess. A similar situation is seen about an otogenous supratentorial fistula which at times is the starting point of subdural suppuration. The details of this situation are to be considered in another study.

*Type 5.*—Subdural abscess consequent to traumatic frontal sinusitis is probably not an uncommon lesion. Local injury to the frontal region not infrequently precipitates acute and often fulminating empyema of the frontal sinus, which in turn results in subdural abscess. This situation is exemplified in case 2 of our series.

*Type 6.*—Subdural abscess secondary to traumatic otitis media and mastoiditis presents a situation similar to that in the foregoing group. Trauma is responsible for enlivening or at times actually provoking the infection in the middle ear and mastoid. In the course of evolution of these lesions a subdural abscess develops in the same manner as in the nontraumatic conditions.

*Type 7.*—Subdural abscess due to rupture into the subdural space of a traumatic abscess of the brain is probably relatively rare, although in the light of the experience of one of us (Courville) the possibility demands some attention. The spontaneous rupture of an abscess into the subdural space occurs but rarely. Of more common occurrence, however, is the extension of pus into the subdural space around a drainage tube surgically placed. One of us (Courville) has observed 2 such cases and also 1 case in which an occipital abscess ruptured into this space after an unsuccessful attempt to drain it.<sup>7</sup> In none of these cases did the abscess chance to be traumatic. One factor militating against spontaneous rupture would be the heavy capsule which forms about most traumatic cerebral abscesses.

From this brief survey of the possible original causative lesions and the pathways of extension of infection to the subdural space, we turn to a brief review of the cases which have come to our personal attention.

#### REPORT OF CASES

*CASE 1.*—*Laceration of the scalp in the frontal region in an infant, due to a fall from a window; infection of the wound with hemolytic streptococci; left hemiparesis, progressive stupor and signs of meningeal irritation; roentgen evidence of osteomyelitis of the frontal bone; death thirty-five days after injury; septic meningitis and subdural abscess over the right frontal lobe.*

A boy aged 1 year was admitted to the Los Angeles County Hospital on Dec. 22, 1934, with a laceration of the scalp due to a fall from a window, the child's head having struck on the edge of some wooden steps. On examination, a deep curved laceration about 5 cm. long, exposing the underlying bone, was found in the right frontal region. Roentgenograms of the skull disclosed no evidence of fracture.

The wound became infected, and drainage persisted in spite of local treatment. Smears and cultures disclosed *Streptococcus haemolyticus* as the infecting organism. The child became restless and irritable and cried more or less continuously. On Jan. 10, 1935, some stiffness of the neck was noted, but no other definite neurologic signs were elicited. On January 23 the child was noted to be lethargic and pale. Complete left hemiparesis was also present. Roentgenograms of the skull showed some irregular rarefaction of bone in the right frontal region, suggestive of osteomyelitis. A lumbar puncture disclosed clear, colorless fluid without an increased number of cells and containing no organisms. The sugar content was normal; a trace of globulin was present.

The child died on January 28, thirty-five days after injury.

An autopsy was performed by Dr. A. F. Wagner, coroner's surgeon, who found a linear fracture of the frontal bone without displacement of fragments. The brain was forwarded to the Cajal Laboratory for further study.

A subdural abscess covering the right frontal lobe had evidently existed some time before death, for yellowish fibrinopurulent exudate was still adherent to the

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7. Courville, C. B., and Cutler, O. I.: Subdural Abscess Secondary to Surgical Drainage of a Cerebral Abscess, *Bull. Los Angeles Neurol. Soc.* 1:114 (Sept.) 1936.

outer surface of the arachnoid over the dorsolateral surface of the lobe. Pus was also present in the corresponding portion of the superior longitudinal fissure.

In addition to the subdural abscess, pus was found within the subarachnoid space (septic meningitis), particularly in the sylvian and basilar cisterns.

There was considerable softening of the entire right frontal lobe and of the central part of the left frontal lobe and the anterior portion of the left corpus striatum, evidently a consequence of occlusion of regional arteries incident to subdural and meningeal infection.

*Comment.*—This case is one of unusual interest in that an infection of the scalp resulted in a subdural abscess (type 2). The infection may have extended either through the local fracture line or by way of regional veins extending through the bone into the superior longitudinal sinus and the afferent superior cerebral veins. Against this conclusion was the absence of gross thrombosis in these veins. The early osteomyelitis was probably a coincident lesion and was not of itself responsible for the subdural abscess and the terminal septic meningitis.

*CASE 2.*—*Focal injury to the head in an automobile accident; fluctuant swelling of the scalp, drained surgically; right hemiparesis; disturbances of speech; jacksonian convulsions on the right side; surgical disclosure of osteomyelitis of the skull in the left parietal region; death three days after exploration; extensive left subdural abscess.*

A white man 59 years of age was admitted to the Los Angeles County Hospital on May 9, 1932, with a boggy infiltration of the scalp about draining surgical wounds in the left parietal region. He had been injured in an automobile accident on January 1, at which time he sustained a contusion of the left side of the head. About three months after his injury he noticed a fluctuant swelling of the scalp in this region. This swelling was opened, and a considerable amount of pus was evacuated. He applied for admission to the hospital because of an elevation of temperature.

On admission, two surgical incisions with rubber drains in place were found in the left parietal region, about which the scalp was edematous and tender. Two days later the patient had a chill and the temperature became elevated. A roentgenogram disclosed mottling of the cranial vault in this region, suggestive of osteomyelitis. A white blood cell count disclosed 8,400 cells per cubic millimeter, 86 per cent of which were polymorphonuclears. The spinal fluid was clear and colorless and was under 150 mm. of pressure. Only 4 cells per cubic millimeter were found. On May 16 the patient complained of weakness of the right extremities and had difficulty in expressing himself. Shortly thereafter he had jacksonian seizures on the right side, followed by generalized convulsions.

An exploratory operation was performed. The bone beneath the surgical opening was found to be softened and eroded, and when a small portion of it was removed the dura was found to be covered with granulation tissue and pus. Drains were placed beneath the bone, radiating away from the defect in the skull. A smear and culture of the pus from the wound showed streptococci and gram-positive bacilli. Because of recurrent convulsions, exaggeration of the right hemiparesis and deepening stupor, the surgical wound in the scalp was reopened. A second opening in the skull was made in a relatively normal area, and the dura was incised. A large amount of pus immediately welled up into the wound. Several drains were placed beneath the dura, and the wound was loosely closed. Cultures from the pus disclosed short chain and long chain streptococci. The

seizures on the right side continued; the patient remained comatose; the temperature remained high and the pulse was rapid. The patient died of intercurrent bronchopneumonia on May 26, one hundred and forty-seven days after the injury.

An autopsy was performed by Dr. John H. Schaefer, coroner's surgeon, who found, in addition to the surgical openings in the skull, a considerable amount of

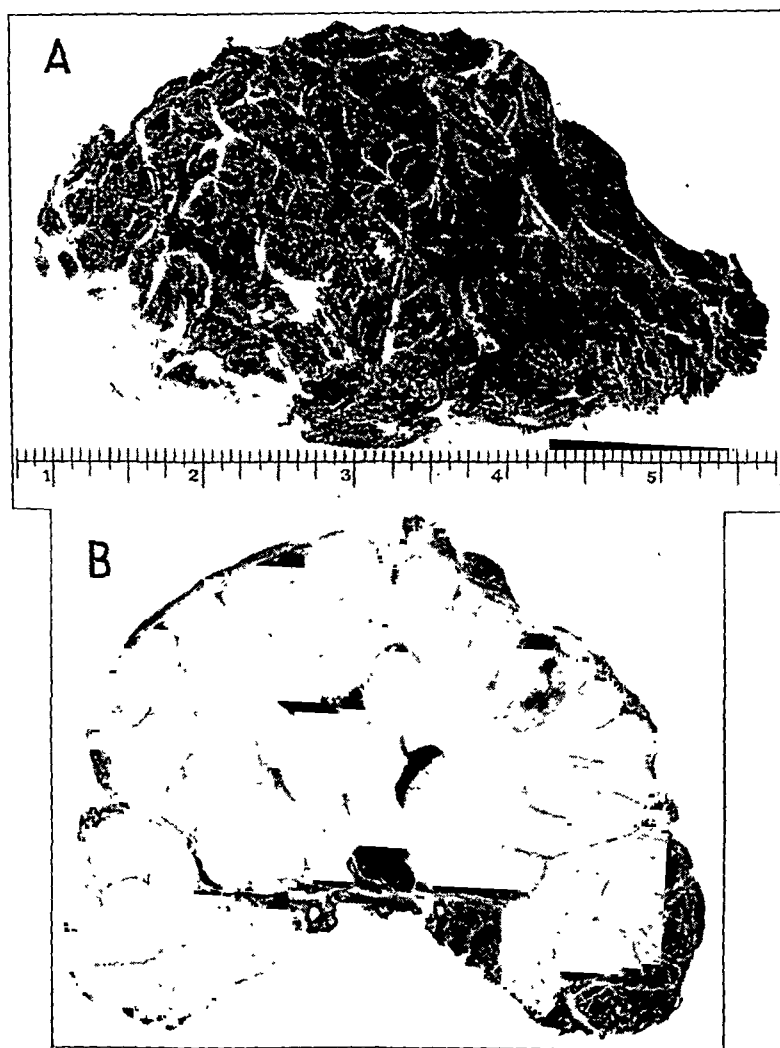


Fig. 1 (case 2).—*A*, fibrinopurulent exudate adherent to the arachnoid over the left side of the brain. *B*, dislocation of the ventricular pattern toward the right side, with dilatation of the contralateral ventricle.

pus in the subdural space. The brain was forwarded to the Cajal Laboratory for further study.

Corresponding to the surgical openings in the skull, the external surface of the dura showed some partially organized granulations in which pus was still present. The inner surface of the dura covering the left cerebral hemisphere was

markedly roughened owing to the presence of fibrinopurulent exudate, which covered most of the dorsolateral surface of the hemisphere and extended to the left side of the falx cerebri and around its inferior margin to its right side.

Adherent to the arachnoid over the left side of the brain was found a fibrinopurulent exudate (fig. 1A). This accumulation of pus in the subdural space resulted in a marked depression of the cortex and a widening of the sulci in this region. The superficial veins in the area were thrombosed, secondary to which red softening of the cortex had taken place. The ventricular pattern was dislocated toward the right side, the contralateral ventricle being dilated (fig. 1B). Petechial hemorrhages were observed beneath the ependyma of the right lateral ventricle.

*Comment.*—The dura and the brain in this case presented the classic picture of subdural abscess. The shaggy appearance of the exudate both on the inner surface of the dura and on the outer surface of the hemisphere was typical. The accumulation of pus resulted in a marked depression of the cortex, especially in the region of the sylvian fissure. The sulci were also widened, as is the rule when cerebrospinal fluid, blood or pus accumulates in the subdural space. Septic thrombosis of the superficial veins with consequent petechial hemorrhages into the cerebral cortex was suggestive of a rather long-standing lesion. The ventricular dislocation with enlargement of the contralateral ventricle was also typical of a large subdural abscess.

*CASE 3.—Injury to the frontal region, sustained in an altercation; fracture of the frontal bone; subsequent cerebrospinal rhinorrhea; mental changes and persistent headaches; intracranial aerocele demonstrated subsequently by roentgenograms of the skull; death from meningitis one hundred and thirty-four days after injury; fracture through the left frontal sinus with communication between the sinus and the subdural spaces; circumscribed subdural abscess.*

A 43 year old Japanese was admitted to the Japanese Hospital in Los Angeles on Feb. 1, 1934, with the complaint of headaches and with evident mental changes. A friend, who gave the history, stated that on the night of Dec. 10, 1933 the patient had been in an automobile collision. In the altercation that followed, he was struck a blow in the left frontal region, falling to the ground unconscious. There were subsequent swelling and ecchymosis of the left eye and left side of the face. The patient bled from the left side of the nose. A roentgenogram of the skull disclosed a vertical linear fracture of the left frontal bone. Shortly after, the patient noticed that clear fluid dripped from his nose when he tipped his head forward.

Aside from the occasional bouts of headache and dizziness, the patient was not seriously disturbed. About a month after the accident the patient's friends became aware that he was becoming careless and forgetful about his work, behaved in an abnormal manner and was in a constant state of unusual good humor.

On his admission to the Japanese Hospital the left eye was prominent and a fracture line in the left frontal region could be easily palpated. There was a slight motor weakness of the right extremities. Roentgen studies of the skull disclosed a large air pocket in the left frontal lobe.

The patient continued to complain of severe headaches; his temperature rose; his mind became cloudy, and he lapsed into coma and died with symptoms of meningitis one hundred and thirty-four days after the original injury. The type of the infecting organism was not learned.

Autopsy, limited to the head, was performed by Dr. C. T. Halburg, of the department of pathology, College of Medical Evangelists. A partially healed double fracture line was found in the left frontal region, with some depression of the intervening fragment. A direct communication (which permitted the interchange of cerebrospinal fluid and air) existed between the frontal sinus and the subdural space. The dura in this region was adherent to the skull, and, in turn, the brain and overlying meninges were adherent to the inner surface of the dura. In lifting the frontal lobes out of the anterior fossae these adhesions were broken, and pus poured out of a circumscribed area of the subdural space which was thus isolated—a localized subdural abscess which measured 2.5 by 6 cm. in its greatest diameters.

The adjacent portion of the frontal lobe was seriously contused. A large sagittally placed air cyst was found in the left frontal lobe. The lateral, the third and the fourth ventricle were all markedly dilated and contained small amounts of purulent exudate, as did the subarachnoid space at the base of the brain.

The type of organism responsible for the intracranial lesions was not learned, material for cultures not being taken at autopsy because the body had been embalmed.

*Comment.*—This case is a classic representative of type 4, in which a subdural abscess is a part of that pathologic complex known as an intracranial aerocele. The infection extends from the adjacent sinus (usually frontal) through the fracture line into the cranial cavity. The inflammatory process is usually limited by adhesions to the immediate vicinity of the cranial opening. In this case the injury to the base was more extensive and a fairly good-sized subdural abscess resulted, although it was definitely localized by adhesions. Extension from such a focus of infection is often responsible for the terminal meningitis, although rupture through its confines may also be responsible for an extensive subdural abscess. We know of no such example of this last eventuality.

*CASE 4.*—Compound comminuted fracture of the cranial vault, sustained in an assault; surgical repair of laceration; discharge from the hospital after sixteen days; readmission in coma; death three months and eleven days after injury; suppurative left frontal sinusitis; extensive left subdural abscess.

A Mexican 36 years old was first admitted to the Los Angeles County Hospital on Jan. 24, 1934, having been assaulted and robbed by two bandits the night before. He had apparently been beaten over the head with the butt of a revolver. On examination, about four hours after the injury, the patient was conscious and rational; nausea and vomiting were evident. Multiple lacerations of the scalp were found in the region of the vertex of the skull and in the left parietal region. A roentgenogram of the skull disclosed a circular comminuted fracture of the left parietal bone, with slight depression. A second rounded, depressed fracture was found at the vertex of the skull posterior to the coronal suture. A third fracture, small and comminuted, without depression, was found in the frontal region.

The wounds were antiseptitized; the depressed fragments were elevated, and the lacerations of the scalp were repaired. The wounds healed without evident infection, and the patient was discharged on February 8 and instructed to return in three weeks.

He was readmitted to the hospital on May 1, 1934, having been sent by the physician at the county jail with the statement that no history of his present illness could be obtained. The patient was semistuporous and when aroused proved to be completely disoriented. He said that this trouble had started three weeks before, but nothing more than this could be learned. He was cyanotic, and his respirations were irregular. No weakness of any of the extremities was observed, although the patient did not seem to be able to control the movement of either lower extremity. Muscular twitching was evident in both arms. No pathologic reflexes were elicited. The neck was rigid. A blood count disclosed leukocytosis, the white cells numbering 14,000 per cubic millimeter, with 68 per cent polymorphonuclears. The spinal fluid was cloudy and under increased pressure (over 400 mm. of water). The cell count was 8,640 per cubic millimeter. A smear disclosed no organisms, and cultures of the fluid proved to be sterile.

The patient became delirious; chills and sweats developed, and death occurred on May 4, one hundred and one days after the injury.

Autopsy was performed by Dr. John H. Schaefer, coroner's surgeon, who found multiple fractures as described. A rather extensive fracture of the left frontal bone extended into the roof of the left orbit, passing through the left frontal sinus, which was filled with purulent exudate. Depression of this fragment permitted a direct communication between the left frontal sinus and the cranial cavity. Greenish pus from the sinus extended directly into the subdural space.

Early bronchopneumonia was also present. The sixth rib on the right side showed an old fracture. A right pleural empyema was also found.

The left cerebral hemisphere was covered with bluish green, foul-smelling pus, suggestive of infection by *Bacillus pyocyaneus*. Smears from the exudate showed streptococci, pneumococci and unidentified rod-shaped organisms. The brain was forwarded to the Cajal Laboratory for further study.

The dorsolateral surface of the left frontal lobe was found to be covered with a heavy fibrinopurulent exudate which obscured the underlying meninges and cortex. The exudate extended laterally along the left sylvian fissure, ventrally onto the basilar surface of the left frontal lobe and across to the adjoining portion of the basilar surface of the right frontal lobe. These areas were depressed, and the regional sulci were widened. Pus covered the medial portion of the basilar surface of the left temporal lobe. The exudate had also extended into the superior longitudinal fissure, covering the entire mesial surface of the left cerebral hemisphere.

The anterior group of superior cerebral veins were thrombosed.

The subarachnoid space, including the basilar cisterns, was filled with pus characteristic of leptomeningitis.

Sections through the brain disclosed a characteristic dislocation of the ventricular pattern. Marked hyperemia of the cerebral substance and petechial hemorrhages in both the gray and the white matter were also found.

*Comment.*—In this case the subdural abscess was a direct consequence of traumatic frontal sinusitis. Depression of a fragment of bone made a direct communication between the sinus and the subdural space. The case seems to be a typical example of post-traumatic subdural abscess of type 5.

*CASE 5.*—*Injury to the right side of the face and head in a fall; cellulitis of the scalp followed by osteomyelitis of the skull; repeated attempts at surgical drainage of multiple abscesses of the right cerebral hemisphere; death two years and three*



*months after original injury; autopsy; healed pachymeningitis interna with multiple abscesses of the right cerebral hemisphere.*

A Mexican boy 10 years of age was admitted to the Los Angeles County Hospital on May 31, 1934, with swelling and marked local tenderness in the right temporal region. The boy had fallen at play eight days before, with injury to the right side of the head, the mastoid region being the part most definitely injured. A swelling had promptly developed in this region, possibly incidental to local minor brush burns. When admitted, he complained of regional pain, inability to close his mouth, stiffness of the neck and fever. Examination showed a reddened right membrana tympani; purulent exudate was coming from the right side of the nose, although the accessory nasal sinuses were clear on transillumination and were roentgenographically normal. Roentgenograms of the skull taken on June 1 were reported to be normal, although when they were reviewed by one of the clinicians what was thought to be a fracture of the skull posterior to the right mastoid was seen. This was not confirmed by subsequent examination.

The right ear drum was opened, but no frank pus was recovered. A culture of material from the ear disclosed *Staphylococcus albus*, presumed to be a contaminant from the canal.

Because of stiffness of the neck a lumbar puncture was done, and purulent spinal fluid under increased pressure was recovered. Cultures of this fluid were sterile, but later ones disclosed *Staph. albus* and *Staphylococcus aureus* as infecting organisms. Repeated spinal drainages resulted in gradual improvement in the patient's condition. The resident otolaryngologist, Dr. A. H. Miller, believed the meningitis to be otitic in origin.

An abscess of the scalp in the right parietal region was opened on June 18, and a culture of the pus showed the infecting organism to be *Staph. aureus*.

On June 25 jacksonian seizures developed on the left side, followed by transitory left hemiparesis.

The patient was first seen by one of us (Courville) on July 7, 1934, by which time multiple abscesses of the right side of the scalp had developed. Aside from a right internal squint, no definite neurologic signs were found. A diagnosis of osteomyelitis of the skull with possible dural involvement (with the residual signs of staphylococcic meningitis) was made. Roentgen examination of the skull two days later disclosed an irregular rarefaction of bone in the right parietal and anterior part of the right occipital bones.

An exploratory operation was done by Dr. Leo J. Adelstein on October 25, and much necrotic bone was removed. Granulation tissue was present external to the dura, which presented several irregular openings through which the cortex had herniated. The dura was also found adherent to the cerebral cortex beneath the area of extradural granulations. An abscess deep in the right temporal lobe was emptied, but a drain could not be inserted. A subsequent attempt at drainage was done on Jan. 7, 1935, by Dr. Adelstein. A parietal abscess was drained on May 24 by Dr. R. B. Raney. After a long convalescence, the patient was discharged from the hospital on December 12, with residual complete spastic left hemiplegia and lowered mentality. On Feb. 10, 1936 a right frontal abscess was drained. The patient recovered from this operation, although persistent and marked left hemiplegia and a gross mental defect betokened an extensive lesion of the right cerebral hemisphere.

The patient died on August 29, shortly after another exploration of the right cerebral hemisphere, twenty-seven months after his injury.

At autopsy there was found an extensive defect in the skull corresponding to the necrotic bone removed at operation almost two years before. The scalp was

adherent to the dura and was separated only with some difficulty. The dura in turn was adherent to the much disorganized cortex of the right frontal, temporal and anterior part of the parietal lobes. Between the dura and the cortex, a layer of organized yellowish exudate was apparent (fig. 2 *A*). In the substance of the hemisphere were found several well encapsulated abscesses as well as a large cyst

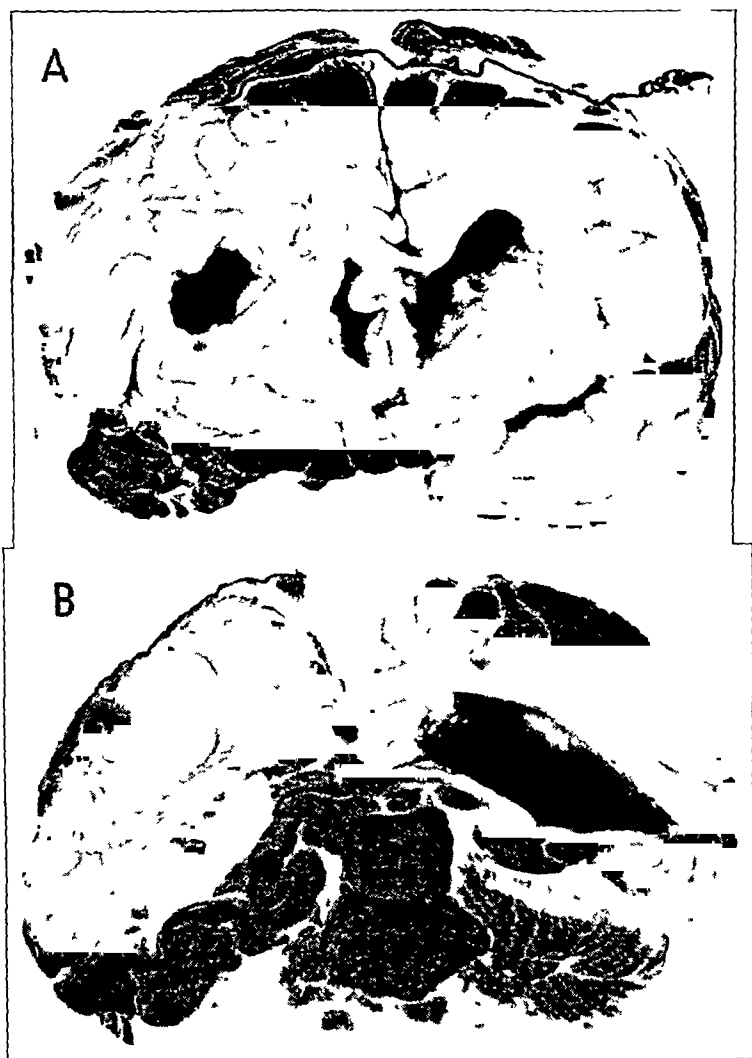


Fig. 2 (case 5).—*A*, layer of organized (yellowish) exudate between the dura and the cortex. A large cyst (filled with yellow fluid) occupies the right external capsule. *B*, section through the splenium of the corpus callosum, showing dural adhesion and small abscess formation.

filled with yellow fluid, which occupied the right external capsule (fig. 2 *B*). In the basilar cisterns was found an accumulation of fibrinopurulent exudate, indicative of terminal basilar meningitis.

*Comment.*—This unusual case presents a number of interesting clinical as well as pathologic aspects. For our purpose the most important clinical problem was the establishment of a causal relation between the trauma and the dural lesion. This seems quite clear, since no other primary lesions were found to account for the subdural infection.

#### ANATOMY OF THE SUBDURAL SPACE

One reason for a lack of proper understanding of traumatic inflammatory lesions affecting the subdural space (*cavum subdurale*) is the imperfect anatomic conception regarding this space. In most textbooks on anatomy little or nothing is said about it, although the peritoneal, pleural and pericardial spaces are discussed in detail. It seems worth while, therefore, briefly to describe the extent, the limitations and reactions of this space to disease processes.

Like the other mesothelium-lined spaces, in the living state this space is a potential one only, since the brain and its system of blood vessels, its membranes and the enclosed cerebrospinal fluid completely fill the cranial cavity. The brain, however, loosely occupies this space, being anchored at the base by the passage of the cranial nerves through the foramens at the base of the skull and by the infundibulum of the hypophysis, in addition to its attachment by entrance of the meningeal arteries and accompanying veins, by the continuation of the medulla with the spinal cord through the foramen magnum and by the entrance of the carotid and vertebral arteries. The brain is also suspended at the vertex by the entrance of the superior cerebral veins and the attachments of the pacchionian granulations; it is less securely held posteriorly and below by the exits of the inferior cerebral and inferior cerebellar veins and the great vein of Galen, which empties into the straight sinus at a point where the inferior margin of the falx cerebri joins the anterior margin of the tentorium cerebelli.

The more intimate relation of the irregular base of the brain with the fossae of the skull, as well as the firm attachment to the cranial base by means of the cranial nerves, makes the *cavum subdurale* in this region a space in name only. Accumulations of foreign material in this region are always small, too small to be of any clinical importance as far as their mass is concerned. A different situation, however, exists over the dorsolateral surface of the cerebral hemispheres. Here the space extends widely without anatomic interruption, which permits large accumulations of cerebrospinal fluid, blood or purulent exudate, sufficient at times to compress the cerebral cortex seriously and to dislocate the cerebral hemispheres and the enclosed ventricular cavities.

The *cavum subdura* is lined with flattened mesothelial cells, one layer forming the lining layer of the membranous structure, the *dura mater*,

and the other the external layers of the arachnoid. In the normal state these two layers are constantly in contact. It is from the mesothelial cells lining this cavity that the neomembrane which envelops any collection of cerebrospinal fluid, blood or pus is formed.

#### PATHOGENESIS OF TRAUMATIC SUBDURAL ABSCESS

Since no experimental work has been done with regard to traumatic dural inflammations, what is written in this connection as to the pathogenesis of subdural abscess must be based on observations made on the pathologic material which has been studied in the Cajal Laboratory. The subject can best be discussed from the point of view of the routes of invasion and of development of the dural lesion itself.

*Routes of Infection.*—On the basis of study of over 60 examples of subdural inflammatory lesions of rhinogenic, otogenic and traumatic origin, it has become obvious to us that infection may reach the subdural space by a number of routes. In the traumatic group in particular the possibilities are varied. The implantation of organisms may be direct or indirect. As has been indicated, direct inoculation of the subdural space must be most unusual, although its possibility must be assumed in case of injury by an edged weapon, which might theoretically open the subdural space alone to infection. It is also possible that a compound fracture, for example, through the frontal sinus with laceration of the dura, might permit an ingress of infected material and that this might be the starting point of a subdural abscess without the interposition of some other intermediate lesion (such as an aerocele). We have encountered no instances of a direct traumatic subdural abscess, although, as has been stated, some of the instances of "pus beneath the dura" described as occurring after saber wounds in the American Civil War might belong to this category.

Indirect invasion of the subdural space is the rule with a traumatic lesion as well as with other types of inflammatory lesion. By indirect invasion is meant an extension of bacteria to the subdural space by some indirect route or method and after an appreciable interval.

The routes of invasion are many. From the original focus of infection in the scalp or accessory nasal sinus the infection may pass through a fracture line or through emissary veins or smaller veins of the calvarium (one or both tables) and the diploic venous system, or it may occur as a consequence of osteomyelitis of the bones of the cranial vault. The infection rarely penetrates the dura directly, as occurs occasionally in the case of intracranial extension in cases of otitis media. It apparently passes by way of the dural sinuses and thence into the afferent superficial cerebral veins to affect the subdural space. It is possible that the infection may reach the subdural space by way of the dural veins without passing through the larger sinuses. If the dura is lacerated, of

course, the infection may extend directly into this space (case 4), but even then the subdural abscess is more often incident to some other inflammatory lesion, a part of an intracranial aerocele (case 3) or consequent to rupture of a cerebral abscess. The possible pathways of infection are shown in figure 3.

*Evolution of the Lesion.*—The nature and the extent of the local subdural lesion depend on the virulence of the invading organism, the

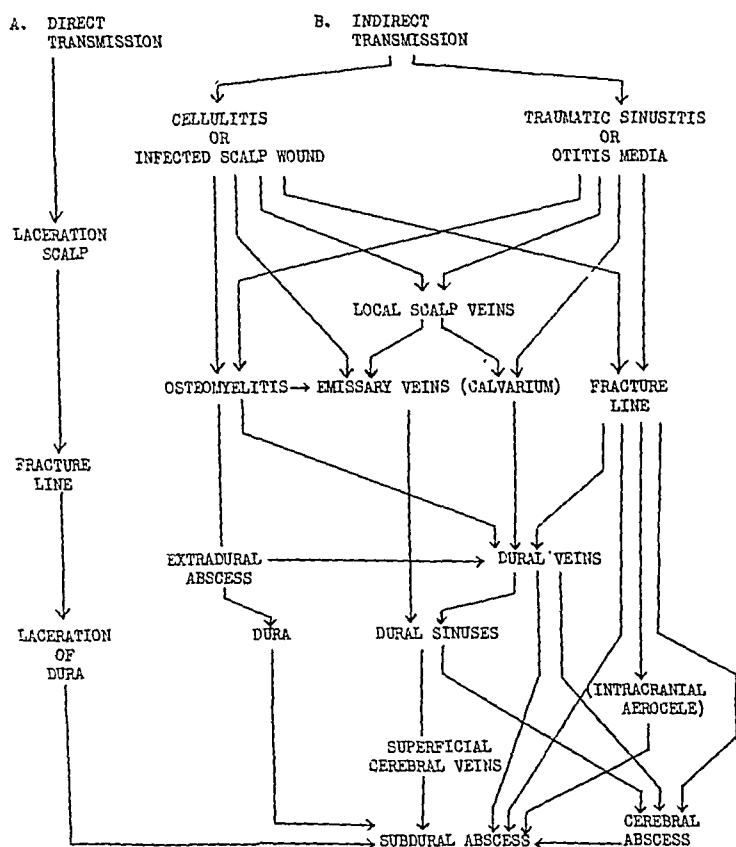


Fig. 3.—Schematic representation of possible pathways of infection.

route of infection and, to some extent, the resistance of the host. Judging from the findings in cases of nontraumatic abscess, the early stages of the lesion are characterized by congestion and exudation on the inner surface of the dura, which appears to be hyperemic and moist and at times presents a local yellowish green discoloration. With low grade infection a local deposit of fibrin develops between the dura and the arachnoid. With more fulminating infections the pus increases in amount and spreads until limited by encapsulation. Suppuration with variable

degrees of organization takes place, and with partial healing adhesions develop between the dura and the leptomeninges. When the process is at all widespread, although the subdural suppuration may be overcome, gross infection of the brain with the formation of multiple abscesses of the brain is the rule. Case 5 is a classic example of this eventuality.

With the more fulminating infections the formation of pus outstrips the local defenses and the space is progressively distended with exudate, which spreads through the space without much interruption. The two factors which tend to limit the spread of pus are (1) fibrin formation and (2) the development of a neomembrane.<sup>8</sup>

The only hope for a patient with a subdural abscess lies in the formation of this membrane (which limits the spread of pus), the acuteness of the attending physician and the wisdom and skill of the surgeon. With limited abscesses, direct drainage without disturbing the limits of this membrane has occasionally resulted in recovery.

#### PATHOLOGY OF SUBDURAL ABSCESS

Subdural abscess is characterized by the presence of variable amounts of fibrinopurulent or purulent exudate in the subdural space, most of which escapes when the dura is opened at operation or at autopsy. This exudate, the color and consistency of which vary with the organism and with the degree of its virulence, commonly accumulates over the anterior and upper portion of the dorsolateral surface of the cerebral hemispheres. Flakes of exudate can be scraped from the under surface of the dura and from the external surface of the arachnoid, a finding which should serve to distinguish the lesion at autopsy from septic meningitis, with which it is frequently confused. The cerebral sulci

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8. The formation of this neomembrane is a subject of great interest. The proliferation of mesothelial cells which go to make up the membrane probably starts as soon as the exudation begins but in many cases is insufficient to prevent the spread of pus in the subdural space. In the fresh state, as when a subdural abscess is exposed at operation, this membrane appears as a thin glistening surface, evident through the surgical aperture in the dura; it may be mistaken under these circumstances for the arachnoid. It is invariably disrupted when the brain is removed at autopsy and therefore is not usually described as part of the lesion observed post mortem.

This membrane is formed by a proliferation of the flattened mesothelial cells lining the dura and possibly from those forming the outer layer of the arachnoid as well. This reaction is not provoked alone by suppurative processes but is seen also with post-traumatic subdural collections of fluid (subdural hygroma) and of blood (chronic subdural hematoma). In the latter case the early thin transparent membrane becomes vascularized from the dura and thickened by the elaboration of connective tissue, resulting in the formation of a characteristic capsule.

are widened, the convolutions being ridged rather than flattened on the side involved. The entire area of cortex covered with exudate is depressed to varying degrees, depending on the amount of fluid exudate.

The extent of the lesion varies considerably, but the upper and anterior portion of the hemisphere is almost invariably covered. In advanced stages the exudate extends from near the frontal pole to as far back as the occipital pole, in which circumstances the upper part of the dorsolateral surface of the temporal lobe is also obscured. At times it extends down into the superior longitudinal fissure, where the pus lies between the falx cerebri and the medial surface of the hemisphere. When it extends across the midline (which is not unusual), it does so in the frontal region, where the inferior margin of the falx cerebri is separated by a small interval from the upper surface of the corpus callosum. Extension usually occurs by way of the furrow of the sylvian fissure and cistern to reach the chiasmal region, which may also be suffused with pus. It is probably in this location that the leptomeningeal space is invaded, although this is usually a terminal event. It is remarkable to what extent the arachnoid prevents the spread of infection to the subarachnoid space, the spinal fluid often showing only a minor degree of pleocytosis until the last.

The cortical structures are partially or completely obscured by exudate even after removal and fixation of the brain. Usually markedly engorged and often partially thrombosed, the superior cerebral veins can be traced beneath the exudate to the superior longitudinal sinus. The exposed portions of the cortex are usually reddened incident to congestion and, at times, to focal subpial hemorrhagic extravasations, giving the surface of the brain a mottled appearance.

The arachnoid enclosing the basilar cisterns may be cloudy with exudate when terminal meningitis has set in.

On section the layer of pus external to the arachnoid is grossly evident, the zone of yellowish material being studded with black spots which indicate cross sections of the thrombosed superficial veins. The subarachnoid space is obliterated owing to the pressure of the exudate. The homolateral ventricle is distorted and flattened; the opposite one is distended. The ventricular pattern is likewise distorted and dislocated toward the contralateral side.

The microscopic characteristics of the lesion are as one would expect. Sections through the dura show a layer of pus and fibrin on its inner surface, the dura itself often being only feebly invaded. Sections from the cortex show a poorly organized exudate external to the arachnoid; in this exudate the causative organism can usually be identified. The subarachnoid space often shows variable degrees of inflammatory reac-

tion, from a mild cellular reaction on one hand to frank meningitis on the other, depending somewhat on the region from which the section is taken.

After healing, a diffuse dense fibrous adhesion binds the dura, leptomeninges and cortex together in a firm union. In this dense scar residual signs of the suppurative process are to be found. In such instances, multiple abscesses of the brain itself are usually found.

#### SUMMARY AND CONCLUSIONS

Traumatic pachymeningitis and subdural abscess are the rarest of intracranial suppurative lesions following injury. Nevertheless, they constitute distinct pathologic entities, which have yet not been given formal recognition in the medical literature.

A classification of the lesions, based on their pathogenesis, is proposed. Seven types of actual or theoretically possible lesions are suggested. Subdural abscess may be (1) due to direct implantation of infected material in the subdural space, (2) due to an extension into the space from a traumatic cellulitis or infected wound, (3) secondary to traumatic osteomyelitis of the skull, (4) a complication of intracranial aerocele, (5) consequent to traumatic frontal sinusitis, (6) consequent to traumatic otitis media or mastoiditis or (7) consequent to rupture into the subdural space of a traumatic abscess of the brain.

A series of 5 cases is reported. The brain in each instance was studied in the Cajal Laboratory. These cases are illustrative of four, possibly five, of the seven possible pathogenetic types of traumatic subdural abscess.

A brief survey of the anatomy of the subdural space is made with respect to its invasion by transudates, exudates and effusions of blood.

The various possible routes of infection to the subdural space are briefly discussed. The likelihood of extension by way of the dural veins and sinuses is emphasized.

The lesion passes through characteristic stages in its evolution, the nature and extent of the ultimate lesion depending on the virulence of the infection.

A subdural abscess consists of a collection of pus imperfectly encapsulated beneath the dura and external to the arachnoid; it is usually limited to the dorsolateral surface of one hemisphere. As a consequence, the underlying sulci are widened, the convolutions ridged and the cortex depressed. The regional cortical veins are frequently thrombosed. The ventricular pattern is characteristically altered and dislocated. The lesion may undergo partial resolution when the infection is less fulminating, but in these circumstances death almost invariably results from multiple abscesses of the affected cerebral hemisphere.



# BASAL CELL CARCINOMA IN YOUTH

## REPORT OF A CASE

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The occurrence of basal cell carcinoma in a person under 20 years of age is extremely rare. A case of such a growth in a girl aged 13 years is presented.

## REPORT OF CASE

P. I., in February 1940, six months before being seen in this clinic, first noticed a small lump in the scalp, directly over the inion. It slowly increased in size but was never painful or otherwise disturbing. Two months later she consulted a physician, who incised the mass. There was no change in the size or progress of the lesion, and it healed over uneventfully. The mass slowly grew larger, and at the time she was first seen by me (in the outpatient department of the Strong Memorial Hospital) it was about 1 cm. in diameter. The surface of the scalp was shiny, and the remnant of the old incisional scar was still in evidence. There was a broad base, and the tumor moved freely with the skin; there was no tenderness. Several hairs grew out of the mass, and many were present around the edges.

The child was referred to the tumor clinic of the hospital, where the impression was that the lesion was probably a papilloma. Wide excision was recommended. The following week excision of the lesion was carried out with the region under local anesthesia, a margin of not less than 2 cm. being left. There was no evidence of involvement of the subcutaneous tissues at operation. The edges of the skin were closed with difficulty, and the wound healed per primam intentionem.

Pathologic examination revealed a distinct basal cell carcinoma, the general topography of which is shown in figure 1. The extension of the tumor tissue far below the basement membrane is noted, but it appears that the entire growth was extirpated. Figure 2 is a view of a section under high power magnification. Here are seen the typical scattered groups of basal type carcinoma cells well below the basement membrane.

After discovery of the nature of the lesion the patient was carefully reexamined. She had always been in good health except for the usual childhood illnesses. There were no other lesions of any kind elsewhere on her body. The remainder of the physical examination was entirely noncontributory except for palpation of a small, easily movable gland in the posterior cervical chain, which had been noticed before operation.

Because of the apparent complete extirpation of the lesion it was thought likely that the girl would have no further difficulty. However, she is to be followed regularly in the tumor clinic.

Barring those tumors which arise from the preexisting lesions of xeroderma pigmentosum, the only case recorded in which the patient

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was younger than the girl in this case was that of Sequeira.<sup>1</sup> In that instance the lesion occurred on the back of a boy of 12 years. The same author<sup>2</sup> recorded occurrence of the lesion in a girl of 15 years.

Two similar cases in which the patients were slightly older children, have been reported. Ewing<sup>3</sup> cited a case reported by Williams; the patient was a 14 year old girl, and the lesion was fatal at the age of 36. Sutton and Sutton<sup>4</sup> recorded the case of a 14 year old boy. Hall and Bagby<sup>5</sup> observed 2 basal cell carcinomas, 1 of the nose and 1 of the face, in patients 22 years old. The reported results of treatment, while



Fig. 1.—Basal cell carcinoma of the scalp with subcutaneous extension.  $\times 7$ .

scanty, indicate that the course is usually as favorable as it is in the older age groups.<sup>6</sup>

1. Sequeira, J. H.: Rodent Ulcer of the Back in a Boy of Twelve, *Brit. J. Dermat.* **2**:391, 1912.

2. Sequeira, J. H.: Dermatological Section of the Royal Society of Medicine, *Brit. J. Dermat.* **21**:57, 1909.

3. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

4. Sutton, R. L., and Sutton, R. L., Jr.: *Diseases of the Skin*, ed. 9, St. Louis, C. V. Mosby Company, 1935.

5. Hall, N., and Bagby, J. W.: Carcinoma in the First Three Decades of Life, *J. A. M. A.* **110**:703 (March 5) 1938.

Several instances of squamous cell carcinoma, excluding those in which the tumor arose from the lesions of xeroderma pigmentosum, in still younger patients have been reported by Abdansky,<sup>7</sup> by Kondratenko,<sup>8</sup> and by New and Hertz,<sup>6</sup> who also saw a 2 year old child with carcinoma of the larynx.

Somewhat similar cases, which have not been classified in either of these groups, are on record. Bellanger<sup>9</sup> saw a girl of 11 years in

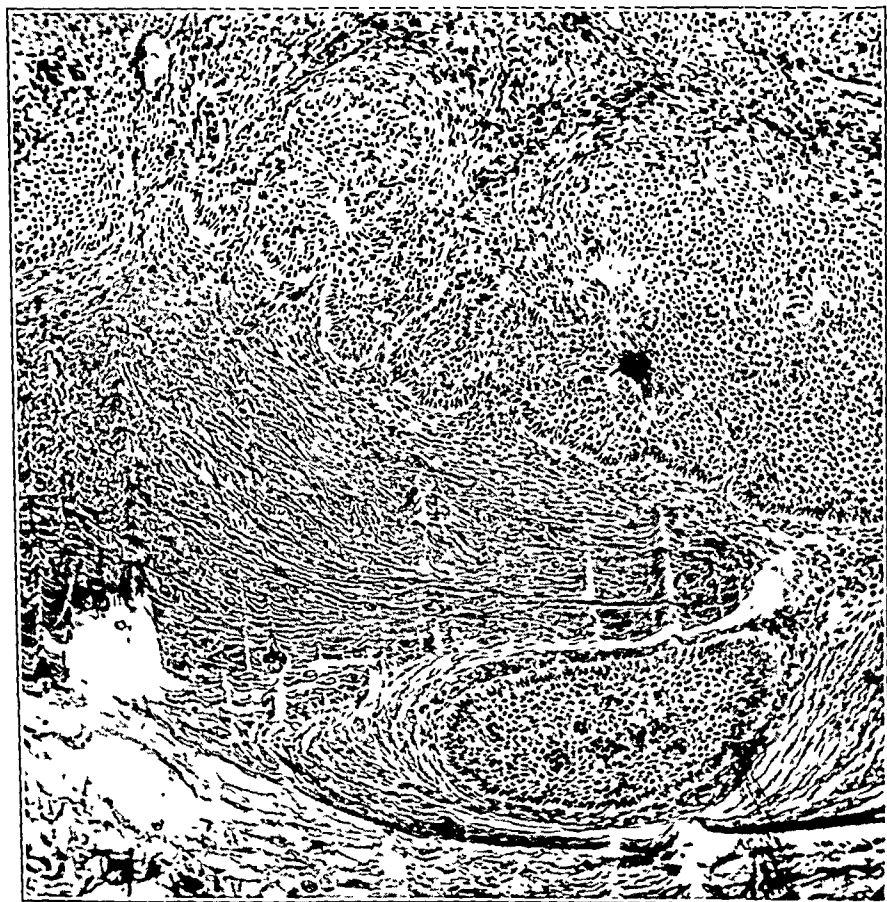


Fig. 2.—Formation typical of basal cell growths.  $\times 100$ .

6. New, G. B., and Hertz, C. S.: Malignant Disease of the Face, Mouth, Pharynx and Larynx in the First Three Decades of Life, Surg., Gynec. & Obst. **70**:163, 1940.

7. Abdansky, A.: Cancer de la lèvre inférieure chez un enfant de neuf ans, Rev. de chir., Paris **52**:557, 1933.

8. Kondratenko, W. A.: Ueber Krebs der Unterlippe bei einem sechsjährigen Knaben, Arch. f. klin. Chir. **168**:431, 1931.

9. Bellanger, H.: Epithélioma calcifié de la peau. Poussées évolutives chez le même sujet, Bull. Assoc. franç. p. l'étude du cancer **24**:467, 1935.

whom several "epitheliomas" appeared over a period of several years. These tumors had areas of degeneration and calcification in the centers. Perin and Blaire<sup>10</sup> recorded a case of "nevocarcinoma" in a child of 3 years.

Since the first description of xeroderma pigmentosum by Kaposi in 1870, the occurrence of tumors in conjunction with the characteristic lesions of the disease has been frequently noted. These have been predominantly squamous cell lesions (Kreibich;<sup>11</sup> Haynes<sup>12</sup>), although Ewing<sup>3</sup> stated that basal cell lesions have been known to occur.

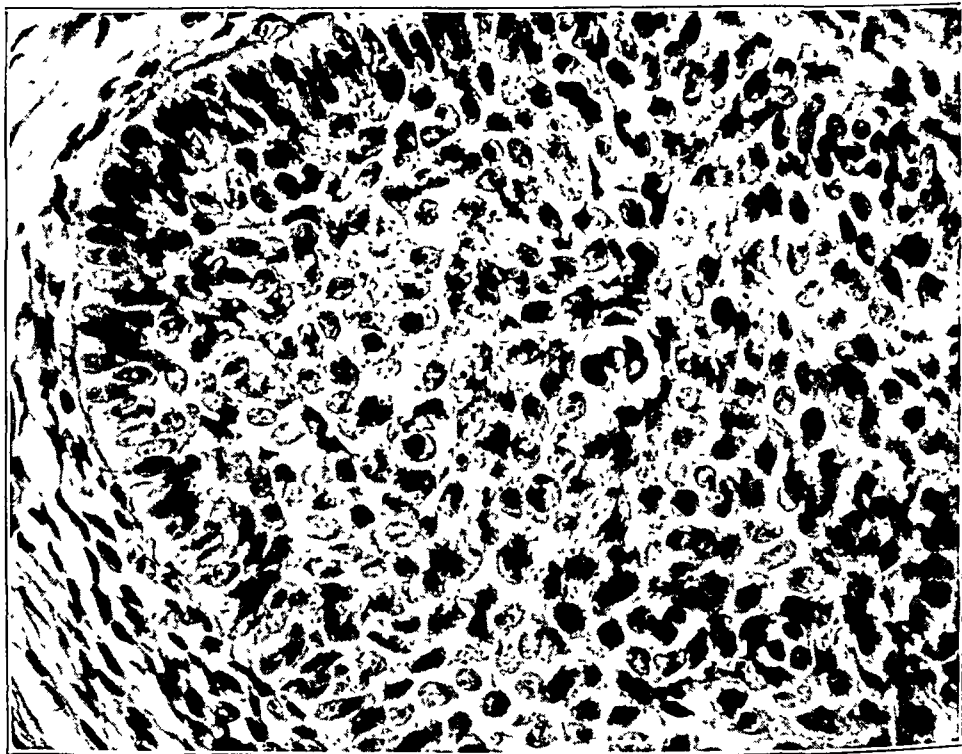


Fig. 3.—High power photomicrograph. The infiltrating tendency seems to be minimal.  $\times 450$ .

#### SUMMARY

The occurrence of epitheliomas in persons under 20 years of age is rare. A basal cell carcinoma occurring in the scalp of a girl of 13 years is described. With adequate treatment the prognosis seems to be as favorable as in the older age groups.

10. Perin, L., and Blaire, G.: Nævo-carcinome de la joue chez un enfant de trois ans, *Rev. franç. de dermat. et de vénéréol.* **13**:491, 1937.

11. Kreibich, K.: Ueber Geschwülste bei Xeroderma pigmentosum Kaposi, *Arch. f. Dermat. u. Syph.* **57**:123, 1901.

12. Haynes, H.: Xeroderma pigmentosum avec épithélioma précoce, *Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg)* **43**:859, 1936.

## TIC DOULOUREUX

### RELATION OF "TRIGGER ZONES" TO PAINFUL SEIZURES; REPORT OF A CASE

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In a previous publication<sup>1</sup> I discussed the advantages of a partial section of the sensory root of the fifth cranial nerve in the treatment of tic douloureux. Careful studies of sensory losses were made post-operatively and correlated with the proportion of root section. It was uniformly and consistently observed that when a third (always the superior-mesial third) of the root was spared the patient was subjectively unaware of any significant sensory loss in the face. Diminution in sensation could be demonstrated by objective tests. The zones of such diminished sensation involved the oral and perioral region—the tongue, gums, buccal mucosa, lips and chin—but even in these zones touch and pain sensibility were not completely abolished. It was my impression that pain sensibility was diminished to a greater degree than was touch sensibility. The zones of diminished sensibility did not agree in extent or configuration with the proposition that each third of the root corresponds with an equivalent peripheral branch in distribution. Corneal sensation was never diminished after a third or a fourth of the root had been left, and so far as I know the painful seizures were permanently cured. Most of these studies were carried out after cutting the root by the cerebellar route. Since that time I have made partial sections by the temporal route and have arrived at the same conclusions.

In attempting to explain why the tic may be cured by partial section of the root, I mentioned the possibility that the trigger zone may be the all-important consideration. Since the trigger zones are practically always oral or perioral and since this is the region of diminished sensibility after partial section, it may well follow that the effect on the trigger zone or zones accounts for the disappearance of the painful seizures. Furthermore, it is recognized that infiltration of procaine hydrochloride into the trigger zones will abolish the pain as long as the anesthesia lasts.

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1. Hyndman, O. R.: Tic Douloureux: Partial Section of the Root of the Fifth Cranial Nerve; a Comparison of the Subtemporal and Cerebellar Approaches from Surgical and Physiologic Standpoints, *Arch. Surg.* **37**:74-99 (July) 1938.

All of the patients whom I studied had pain in the second and third branch distribution, and I was unable to obtain information concerning the effect of partial section on the pain of ophthalmic distribution. The following case is interesting not only because the painful seizures were limited to ophthalmic distribution but because the patient had discovered definite trigger zones on the gums and lower lip on the same side.

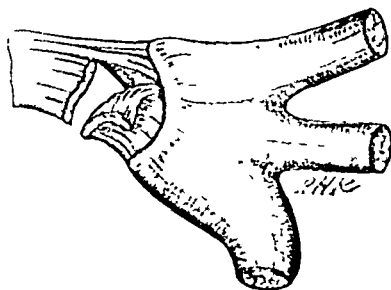


Fig. 1.—Drawing to illustrate the proportion of fibers of the sensory root that were sectioned. The superior fourth of the root was spared. The motor root is shown mesial to the sensory root as it courses diagonal to the fibers of the latter.

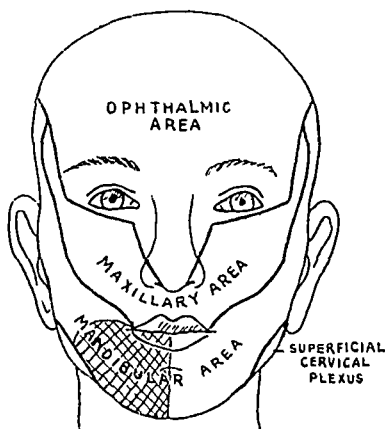


Fig. 2.—Diagram to illustrate the sensory disturbance incurred by partial section of the sensory root of the fifth cranial nerve. In the cross-hatched zone sensibility to touch, pain and temperature was largely but not entirely abolished. Outside this zone sensation was not disturbed. Corneal sensation and motor function were intact. Sensory losses inside the mouth are discussed in the text.

#### REPORT OF CASE

F. R., a white man aged 72, came to the hospital on April 2, 1940. For a little over three months he had experienced attacks of sharp, lancinating pain in the forehead, above the right eye. The seizures began and ended suddenly, never lasting over ten to fifteen seconds. There was no pain between attacks, but the

attacks had become frequent, occurring nearly every fifteen minutes. His son stated that he was a stoic, hard-working farmer who paid little attention to ordinary pain but that he had almost been driven to desperation by this. He could not eat or open his mouth to talk without being thrown into the agony of a seizure.

*Examination.*—The general and neurologic examination gave essentially negative results. The patient had the apprehensive expression that characterizes tic douloureux and was reluctant to talk for fear of a seizure. He stated that if anything touched his gums or lower lip on the right he would be seized with pain. He demonstrated by touching the right side of his lower gum with his finger and immediately was seized with pain in the right side of the forehead which caused him to press both hands firmly against it and brought tears. He had several such seizures while in the office, their duration being ten to fifteen seconds. He repeatedly and emphatically denied that he had ever had pain in the trigger zones or indeed below the right eye.

*Operation.*—On April 3 the sensory root of the right fifth nerve was partially sectioned as shown in figure 1. Special care was taken to cut the filaments and to avoid pulling or tugging on the root. About three fourths of the sensory root was cut, two small superior bundles being left. The motor root was spared.

*Course and Postoperative Examination.*—The patient made an unevenful recovery and has been completely free from seizures to the time of writing (seven months). While he was in the hospital and on follow-up examination, twenty-six days after the operation, the findings were as follows: Subjectively his gums on the right felt numb and the right side of his chin somewhat numb. There was not sufficient numbness, however, to be in the least disturbing. Objectively the sensibility to touch and pain on the right anterior aspect of the tongue was about 50 per cent of that on the left. Both the upper and the lower gums on the right side retained about 20 per cent sensation, being more sensitive to touch than to pain. Sensibility to pain, touch and heat was almost but not entirely lost over the right side of the chin (fig. 2). No diminution in sensation could be elicited elsewhere. Corneal sensation was not impaired, and motor function of the fifth nerve was intact.

#### COMMENT

This case is another illustration of the favorable discrepancy between the proportion of sensory root cut and the diminution of sensation in its distribution. Section of the lower two thirds of the sensory root does not result in sensory losses corresponding to those observed after section of the second and third peripheral branches of the fifth nerve. When interrupting the fibers of the sensory root one should cut the filaments or sever them in such a way as to preclude any possibility of avulsing the entire root. If a large portion of the root is tugged on with a hook, it is quite possible that more of the root will be avulsed at the pons than is bargained for, and hence the sensory losses may be greater than necessary.

Of equal interest and importance is the fact that this patient had pain limited to the ophthalmic distribution and yet had discovered oral trigger zones in the usual locations. A partial section of the sensory root, which greatly diminished sensibility in these trigger zones, abolished the painful seizures. This rare case seems to indicate clearly

that the trigger zones of tic douloureux may be independent in location from the region of referred pain, and if the trigger zones are rendered insensible the tic will be eliminated regardless of its location.

#### SUMMARY

A case of tic douloureux is presented in which the painful seizures were limited to an ophthalmic distribution. Trigger zones, however, were located about the gums and lower lip. A partial section of the fifth sensory root, which resulted in diminution of sensation only in the mouth and on the chin, abolished the tic. A possible relation between the trigger zones and the referred pain is discussed.



# DIFFERENTIAL SENSITIVITY OF SARCOMA AND NORMAL TISSUES TO TEMPORARY ARREST OF CIRCULATION

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AND

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MINNEAPOLIS

Warburg, Wind and Negelein<sup>1</sup> suggested that tumor cells should be particularly sensitive to lack of nutrition because of their high metabolic rate. This conception seems to be borne out by the fact that Jensen's sarcoma undergoes extensive necrosis in rats which are exposed to 5 per cent oxygen for forty hours.<sup>1</sup> Okamoto<sup>2</sup> and Warburg, Wind and Negelein<sup>1</sup> have shown that tumor cells remain viable after prolonged exposure to environments lacking either dextrose or oxygen. In a medium lacking both dextrose and oxygen, however, tumor cells die very rapidly; so it was found impossible to transplant the Jensen sarcoma after only four hours in such a medium. Furthermore, when a tumor-bearing animal was killed and kept at 37 C. for four hours after death, slices of tumor tissue placed in a medium containing dextrose and oxygen no longer metabolized, indicating irreversible destruction of the tumor cells.<sup>1</sup>

On the basis of evidence presented by Warburg, it seemed worth while to investigate the differential susceptibility of tumors and of normal tissues to temporary complete arrest of the circulation. When the arterial flow is stopped completely, oxygen is used up at a relatively rapid rate, and the cells continue to derive energy anaerobically, while metabolites accumulate in the tissues. Differences in sensitivity of cells to irreversible damage by stasis depend on the rate of cellular respiration, the capacity for anaerobic metabolism, the ability to buffer accumulating acid wastes and the specific characteristics of the autolytic

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1. Warburg, O.; Wind, F., and Negelein, E.: Ueber den Stoffwechsel der Tumoren im Körper, *Klin. Wchnschr.* **5**:529, 1926.

2. Okamoto, Y.: Ueber Anaerobiose von Tumorgewebe, *Biochem. Ztschr.* **160**:52, 1926.

enzyme systems. Some consideration was given to the possibility that should tumor tissue prove to be more sensitive than normal tissue to arrest of the circulation temporary stasis might become of value as a therapeutic procedure.

Allen<sup>3</sup> claimed that temporary interruption of the blood supply caused diminution in size or "cure" of 3 fibromas in rats, 1 carcinoma in a mouse and 2 carcinomas in human beings. The author also referred to his previous work, in which he claimed analogous results with three types of transplantable tumors in rats, mice and chickens. Allen also mentioned numerous other experimental tumors which were treated with temporary stasis with inconclusive results.<sup>4</sup> We have treated 26 experimental tumors in rats with temporary stasis, but in no case did we observe a cure of the tumor in the sense of macroscopic disappearance of the tumor and absence of viable malignant cells on microscopic examination.

#### METHODS

Sixty rats about 3 months of age, some albinos of the genetically pure "La Jolla" strain and some hooded, were used in these experiments. Five milligrams of methylcholanthrene dissolved in 1 cc. of melted lard was injected subcutaneously into the left hindleg of each of the animals. The carcinogenic substance acted promptly, and about 50 of the animals exhibited distinctly palpable tumors three months after the injection. A number of animals were lost because of respiratory difficulties in the course of anesthesia with pentobarbital sodium. In order to avoid accidents of this type, later only very light ether anesthesia was employed during the establishment of arrest of blood flow. The circulation to the tumor-bearing leg was at first interrupted by simple ligation with heavy thread, which proved impractical because arterial blood flow established itself soon after the ligatures were applied and the legs became very edematous. In order to interrupt the trickle of arterial blood which continued to supply the leg with some nourishment, rubber ligatures were tried. By this method blood flow was interrupted completely, but in most cases the normal circulation was not reestablished after termination of the experiment, and the whole leg became gangrenous. Our main body of experiments was undertaken with inflatable cuffs analogous to blood pressure cuffs but of smaller dimensions, to fit the thigh of the rat. The leg was slipped through the cuff until the tumor was well below the pressure zone. The cuff was then inflated to a pressure of 250 to 300 mm. of mercury. This procedure interrupted the blood supply of the leg and the tumor efficiently; the leg became cold and cyanotic, and no edema developed during the experimental period. The quantity of blood which continued to flow through the femur was obviously negligible. The rats were prevented from removing or chewing their cuffs by confinement of the opposite hindleg and by means of a large wooden collar similar to the traditional New England stock used for punishing minor offenses.

3. Allen, F. M.: Effects of Local Reaction in Spontaneous Tumors of Animals and Human Beings, *Arch. Surg.* **41**:79 (July) 1940.

4. Allen, F. M.: Influence of Local Asphyxia, Organ Extracts and Temperature Changes on Engrafted Subcutaneous and Visceral Tumors in Rats, *Urol. & Cutan. Rev.* **44**:12, 1940. Allen, F. M.: Ligation Treatment of Chicken Sarcoma, *M. Rec.* **152**:87, 1940.

The rats withstood this procedure well, and there were no casualties during the period of stasis. After termination of the experiment the animals were kept in an air-conditioned room, the temperature of which was kept at 82 F. Food and water were available in the cages. It was found that rats would tolerate a period of seven hours of interruption of blood supply to the tumor-bearing leg. Seven and one-half hours of stasis resulted in death of the animal from one to seven days after the experiment. The cause of death could not be ascertained at autopsy. All rats subjected to eight hours of anemia died within twelve hours, presumably of shock. Most experiments were undertaken with periods of stasis of six to seven hours in order to keep the animal alive for some time after exposure to the longest possible period of stasis.

The rats were killed after a variable period of survival. Autopsy was performed on the hindleg, and the sarcoma and the surrounding normal tissues were fixed in solution of formaldehyde and embedded in paraffin. The blocks were sectioned serially at 8 microns, every hundredth section being mounted and stained with hematoxylin and eosin. Untreated control tumors, corresponding to each group of experiments, were also studied grossly and microscopically.

#### RESULTS

*Six Hours of Complete Arrest of Circulation.*—Nine tumors were subjected to six hours of stasis. The experiments were undertaken four months after injection of the carcinogenic agent. The tumors were firm and varied in size from  $\frac{1}{4}$  by  $\frac{1}{4}$  inch (0.6 by 0.6 cm.) to  $\frac{3}{4}$  by  $\frac{3}{4}$  inch (1.9 by 1.9 cm.). More accurate measurements were not possible because of the location of some of the tumors, which were growing into the musculature of the leg. Four animals were killed three days after termination of the experiment (rats 1 to 4); 3 animals were kept alive for nine days (rats 5 to 7), and 2 animals were kept alive for thirty-two days (rats 8 and 9). After removal of the pressure cuff, circulation was reestablished almost immediately. The animals at this stage exhibited increased lacrimation and were abnormally thirsty. One day after the period of stasis the leg was warm and somewhat edematous; after three days the previously anemic limb appeared normal and had recovered its function.

The tumors had changed in some cases from the previous firmness to a softer consistency. The tumors of the animals which were kept alive for some time continued to increase in size, as was seen in the animals which survived for thirty-two days. These tumors no longer passed through the cuff at the time the animals were killed, because they had grown to such large dimensions in the thirty-two days following stasis.

RAT 1.—The animal was killed three days after anemia was produced. The tumor showed an extensive central area of necrosis (fig. 1). The tumor was composed of a variety of cytologic types—fusiform cells, giant cells and round cells. Tumor tissue was seen infiltrating the muscle tissue and enveloping the muscle fibers. The peripheral portions of the tumor appeared normal. In the necrotic

area occasional viable tumor cells were seen. The noninfiltrated muscle looked normal, although there was some inflammation as well as widening of the spaces between muscle fibers. In some areas hemorrhage into the tumor was evident. A nerve trunk included in the anemic area was invaded by macrophages and appeared somewhat edematous. The dimensions of the tumor were approximately  $\frac{1}{2}$  by  $\frac{1}{2}$  inch (12 by 12 cm.).



Fig. 1 (rat 1).—Condition after six hours of complete anemia of the hindleg. The right lower corner of the illustration shows a small part of the necrotic area. The rest of the picture shows apparently viable tumor cells.

RAT 2.—The rat was killed three days after anemia was produced. The tumor was similar to that of rat 1. Areas of complete necrosis of hyaline appearance alternated with apparently viable tumor tissue. There were all intermediate stages between these extremes, with and without inflammatory reaction. In some areas different types of tumor cells seemed to exhibit a differential resistance, nearly all of the polynuclear giant cells showing extensive central necrosis, while the fusiform cells remained viable in areas in which all other types of cells were necrotic. The muscle cells were apparently normal. In some regions the tumor was sharply

delineated from the surrounding tissues, while in others it was infiltrating the latter. The tumor was approximately the size of a large bean.

RATS 3 AND 4.—These were similar to the others. The animals were killed three days after the production of anemia. There were only minor variations of the pattern of distribution of healthy and necrotic tissue in the sarcoma. The dead cells were situated almost entirely centrally, and the viable portions of the tumor were in the periphery. Some of the nerve trunks included in the sections showed inflammatory infiltration and edema.

RAT 5.—The rat was killed nine days after the production of stasis. Extensive central necrosis with apparently viable peripheral areas was observed on examination of the sarcoma. In portions of the necrotic area a mucoid hyaline substance was seen. No organization of the necrotic area was observed.

RAT 6.—The rat was killed nine days after the experiment. The tumor showed a few central necrotic areas and peripheral regions with viable tumor cells invading normal muscle. In nerve trunks, there was some invasion of tumor cells into the perineurium and vacuolation of axis-cylinders.

RAT 7.—The animal was killed nine days after anemia was produced. No essential difference between this tumor and the others of the same group was observed.

RAT 8.—The animal was killed thirty-two days after arrest of the circulation. Extensive central necrosis was evident. Viable tumor cells were seen infiltrating normal muscle and adipose tissue.

RAT 9.—The animal was killed thirty-two days after the production of stasis. This tumor was the size of a cherry, with a central mass of tissue which consisted of debris and necrotic cells, the outlines of which were still clearly recognizable. This was interspersed with viable tumor cells and with leukocytes. The surrounding muscle was atrophic in some regions and normal in others. The peripheral portion of the tumor was made up almost entirely of viable tumor cells.

*Seven Hours of Complete Arrest of Circulation.*—A group of 4 tumors was subjected to seven hours of stasis five months after injection of the carcinogenic substance. The tumors were 1 by 1 inch (2.5 by 2.5 cm.) in size. Three animals were killed for autopsy eight days after the period of stasis, and 1 animal, nine days after the experiment. The function of the leg seemed to be restored within three days. During the first two days after stasis the animals looked sick and did not eat, although they drank a large volume of water. The experimental leg appeared normal at autopsy except for some thickening of the subcutaneous connective tissue.

RAT 10.—The border of the central necrotic zone and the normal tumor tissue was sharply defined. The surrounding zone of viable tumor tissue was broad. The central necrotic zone showed preservation of the general structure of the tissue, although karyorrhexis was complete. The peripheral viable tumor tissue appeared to be surrounded by a fibrous capsule, but close inspection showed that the surrounding muscles were infiltrated by vital tumor cells. The muscle fibers in the infiltrated areas were often atrophic.

RAT 11.—Necrotic and vital areas alternated throughout the central portion of the tumor. The peripheral parts of the tumor seemed to be viable. The infiltrated muscle appeared necrotic.

RAT 12.—The entire central area of the large (1 by 1 inch [2.5 by 2.5 cm.]) tumor was necrotic. A very thin margin of viable tumor cells surrounded the necrotic area (fig. 2). The viable cells were in contact with muscle fibers, which seemed to be undergoing compression atrophy.

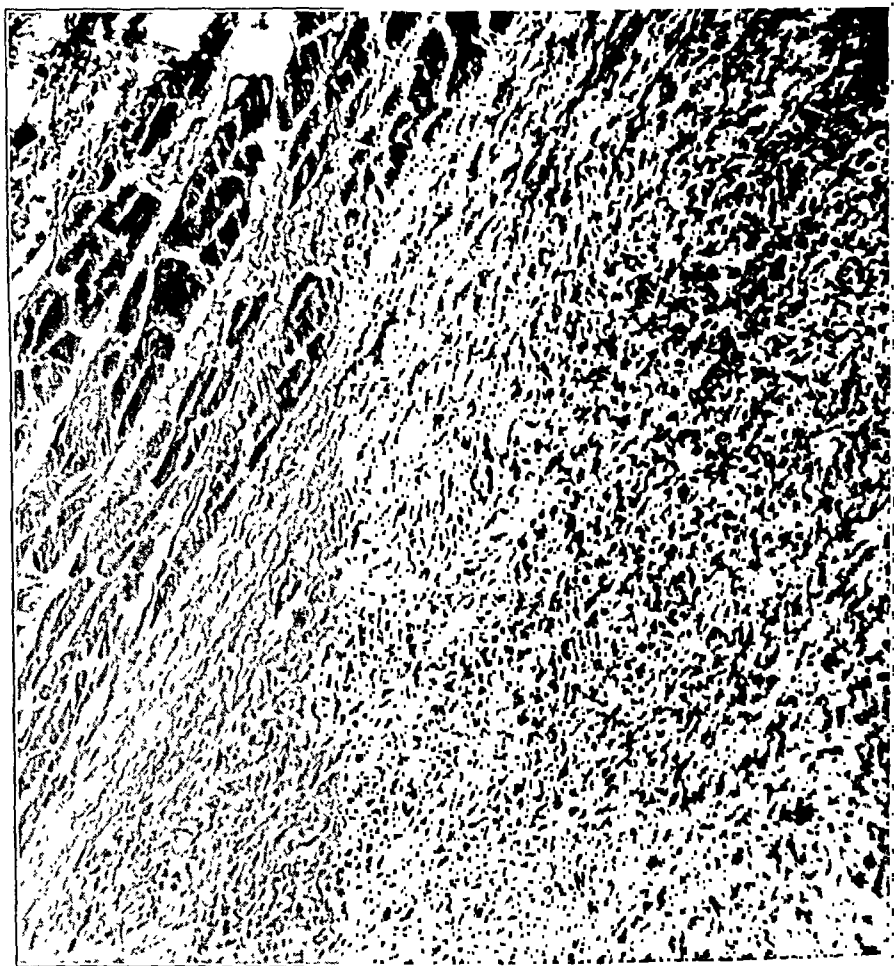


Fig. 2 (rat 12).—Condition after seven hours of complete anemia of the hindleg. This illustrates the debris-strewn central necrotic area. Viable tumor cells can be seen in proximity to the compressed muscle fibers in the left upper quadrant.

RAT 13.—The tumor consisted of several hyaline eosinophilic necrotic areas, surrounded by muscle which seemed to be undergoing pressure atrophy and was infiltrated with viable tumor cells. Nerve trunks which were embedded in tumor tissue did not show significant changes.

*Seven and One-Half Hours of Arrest of Circulation.*—The tumors were of approximately the same size as those in the group just described.

The experiment was performed five months after injection of the carcinogenic material. The function of the leg was restored several days after the experiment.

RAT 14.—This animal died within twelve hours after termination of the experiment. Grossly the leg was edematous and showed numerous hemorrhagic areas. The tumor was the size of a walnut. The central areas were necrotic and



Fig. 3 (rat 17).—Condition after seven and one-half hours of complete anemia of the hindleg. This illustrates a section of the capsule surrounding the central necrotic area. A nerve trunk is seen in the left lower quadrant. Necrotic giant cells are present in the left upper quadrant.

hemorrhagic. At the periphery viable tumor cells could be seen. The surrounding muscle fibers showed pronounced edema but otherwise appeared normal. It was not easy to distinguish viable from necrotic areas in this tumor, because karyorrhexis had only begun.

RAT 15.—The animal died two days after termination of the experiment. The tumor was the size of a hazelnut. It was almost wholly necrotic, but isolated

viable cells could be observed, especially in regions where the tumor had infiltrated muscle tissue. The muscle fibers appeared necrotic.

RAT 16.—The animal died eight days after the experiment, and the anemic leg had recovered some of its function. The tumor was approximately  $\frac{1}{2}$  by  $\frac{1}{2}$  inch (1.2 by 1.2 cm.) in size. The major portion was composed of a tissue in which necrotic cells and viable cells were mixed in about equal proportion. The periph-

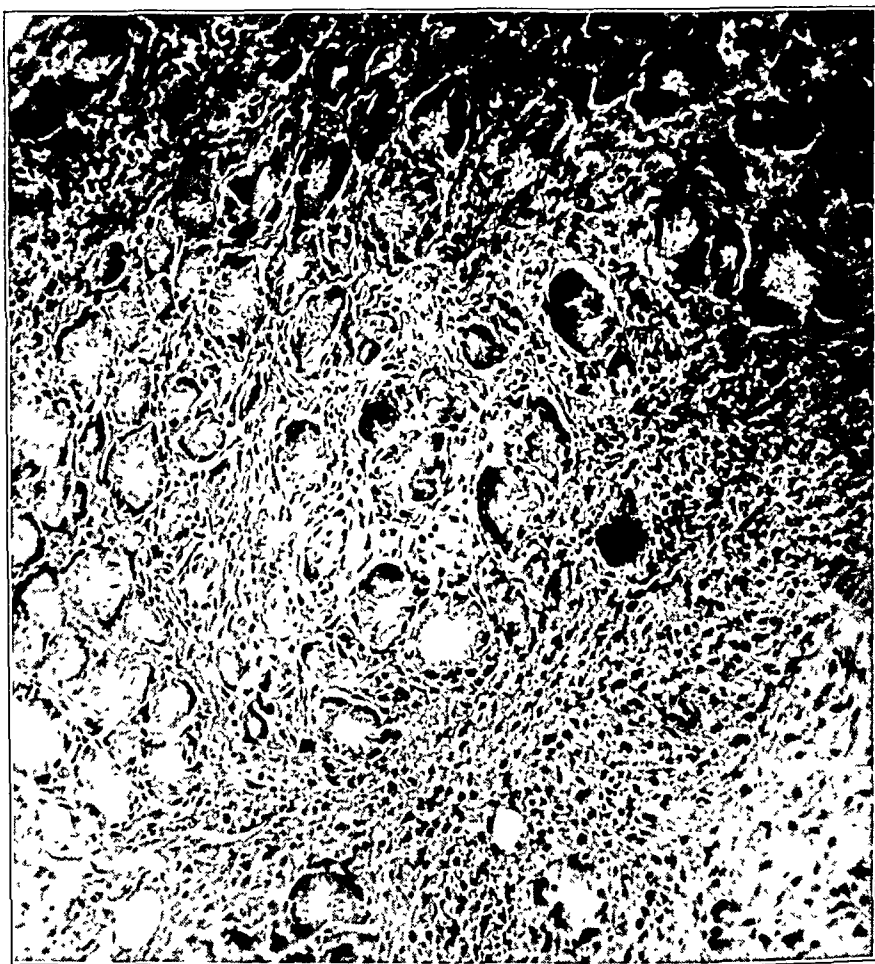


Fig. 4 (rat 18).—Condition after twelve hours of incomplete arrest of the circulation to the hindleg. Necrosis is evident in the giant cells, but most of the other tumor cells seem to be viable.

eral part of the tumor was composed of viable cells which infiltrated atrophic-looking muscle tissue. The nearby noninfiltrated muscle looked quite normal except for somewhat dilated tissue spaces.

RAT 17.—The animal was killed eight days after the experiment. Good function of the leg was observed at this time. The tumor ( $\frac{1}{2}$  by  $\frac{1}{2}$  inch [1.2 by 1.2 cm.]) consisted of a large central necrotic area surrounded by a very thin zone of fibrous tissue which was infiltrated by viable tumor cells (fig. 3). Muscle in



contact with this peripheral tumor zone showed an increase of vacuolated areolar tissue. The muscle fibers appeared normal. There was little inflammatory reaction.

*Eight Hours of Complete Anemia.*—Four rats with tumors were subjected to eight hours of complete arrest of the circulation to the hindlimb. The carcinogenic material had been injected five months



Fig. 5 (rat 27).—Untreated control tumor six weeks after injection of methylcholanthrene. Note the intact giant cells.

before. All of these animals died, presumably of shock, within twelve hours after restoration of blood flow in the leg. No gross pathologic change that could account for death on any other basis than shock was observed at necropsy.

*Twelve Hours of Incomplete Anemia.*—Nine tumors were subjected to incomplete arrest of the circulation for twelve hours. The tumor-bearing leg was rendered ischemic by a ligature of ordinary string.

which caused the limb to swell considerably and to become cyanotic during the experiment. This is interpreted as indicating reestablishment of some degree of arterial flow associated with venous obstruction. Except for this arterial flow, which could not have exceeded the increase in volume of the leg, the tumors were anemic for twelve hours. The

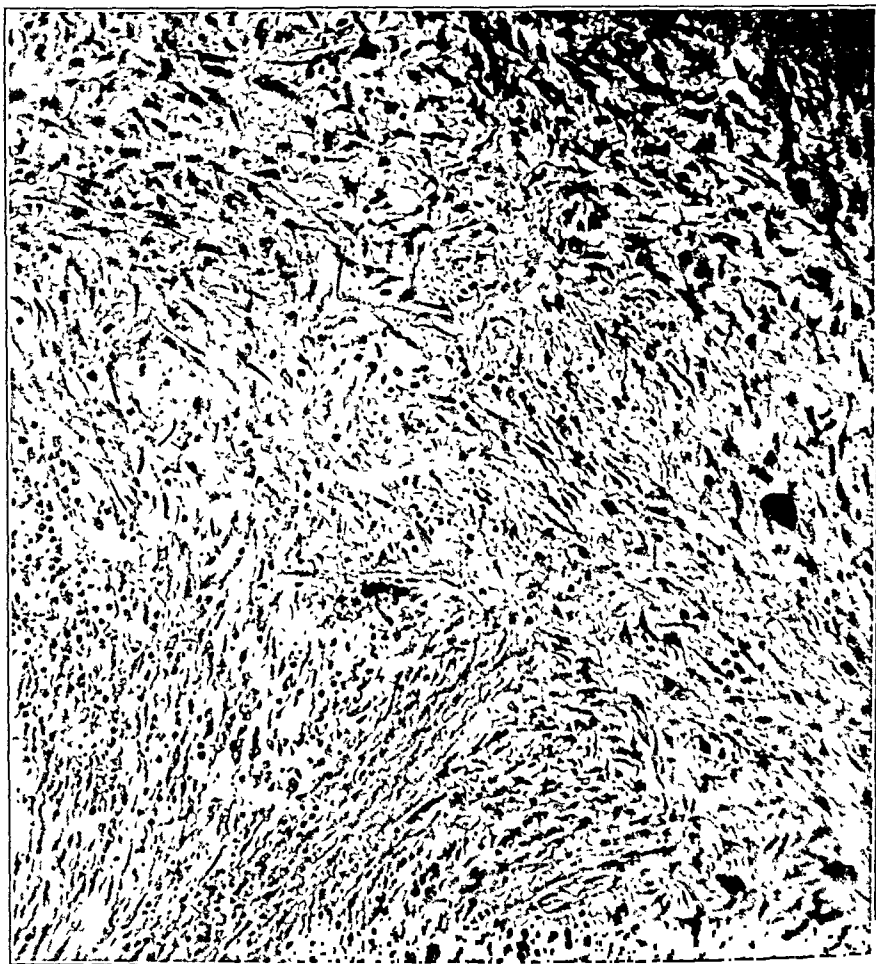


Fig. 6 (rat 31).—Untreated control tumor five months after injection of methylcholanthrene.

experiment was performed six weeks after injection of the carcinogenic substance, when the tumors were the size of small peas. Autopsy was performed on some animals three days and on others eight days after the experiment. The legs were then still edematous but not cyanotic. Their function did not seem to be completely reestablished.

RATS 18 AND 19.—The animals were killed three days after the experiment. The tumors showed some necrotic areas and some other regions in which it was difficult to distinguish between viable and necrotic cells (fig. 4). Much of the

tumor tissue appeared viable. The tumor and some of the surrounding tissue were infiltrated with inflammatory exudate. The surrounding muscle was edematous, and the fibers showed cloudy swelling.

RATS 20 TO 26.—These animals were killed eight days after the experiment. The muscular tissue of the legs showed definite retrogressive changes, such as disappearance of striation, fragmentation of fibers and inflammation. The tumors showed much necrotic tissue, but viable tumor cells could be found in every slide, especially in the periphery, where the tumors were in contact with the surrounding musculature and areolar tissue.

*Untreated Controls.*—The following observations were made:

RATS 27 AND 28.—Injection of methylcholanthrene was done six weeks before autopsy. Macroscopically the tumors were small specks (1 by 1 mm.) of pigmented tissue surrounding the site of injection in the otherwise normal leg. Malignant cells were seen to arise in the fibrous capsule which surrounded the injected material. Just outside the fibrous capsule were seen intact polynuclear giant cells surrounded by nests of smaller tumor cells (fig. 5). There was incipient infiltration of tumor cells into the intact musculature.

RATS 29 AND 30.—These control animals were killed seven weeks after injection of methylcholanthrene. The tumor consisted of a capsule of loose areolar tissue which surrounded the injected carcinogenic substance. Giant cells and round cells were seen in this connective tissue, and tumor cells were seen to infiltrate adjoining muscles. There were necrotic areas in the tumor, and many of the giant cells showed slight spontaneous central necrosis.

RATS 31 TO 34.—Methylcholanthrene was injected five months before autopsy. The tumors (fig. 6) were typical large polymorphic sarcomas (1 to 1½ inches [2.5 to 3.7 cm.] in diameter on the average). The tumors presented some degree of necrosis, but the necrotic areas were very small compared with the necrotic areas in the tumors subjected to stasis. A rough estimate indicated that in the control tumors the ratio of normal to necrotic tissue was about 10:1, while in the tumors subjected to prolonged stasis the same ratio was 1:10 or even less.

#### COMMENT

Complete arrest of the circulation for periods of six to seven and one-half hours leads to extensive necrosis of tumor tissue and marked reduction in the number of viable tumor cells. In no case, however, did we observe complete disappearance of tumor cells. The other tissues, except for minor alterations, did not seem to be severely affected by this procedure. It was impossible to extend the period of stasis beyond the limits reached in the aforementioned experiment, not because the damage to the normal tissues would have been too extensive<sup>5</sup> but because the animal would have been killed by the shock.

This is borne out by our observations on eight hours of stasis in the hindleg as well as by the studies of Allen,<sup>6</sup> who found that rats

5. Allen, F. M.: The Tourniquet and Local Asphyxia, *Am. J. Surg.* **41**:192, 1938.

6. Allen, F. M.: Physical and Toxic Factors in Shock, *Arch. Surg.* **38**:155 (Jan.) 1939.

invariably died of shock after five hours of complete anemia of one hind-leg. Allen suggested that the shock in this experiment was induced by toxin from the tissues which had been rendered anemic as well as by the loss of fluid into the local tissue spaces.

In clinical cases of tumor in which the symptoms are due to the large size of the tumor, some relief might be expected from the stasis method of treatment. On the other hand, this treatment seems unable to destroy the tumor cells selectively and completely, and recurrences and further metastatic growth are inevitable.

It is interesting to note the almost exclusive survival of tumor cells in the periphery, where they are in contact with the musculature. One possibility is that the older central tumor cells, as a result of changes in metabolism, have become more susceptible to arrest of circulation than are the younger, more rapidly proliferating peripheral cells. Another possibility is that muscle fibers supply some energy-yielding substance for anaerobic metabolism to the adjacent peripheral tumor cells. In any case, it seems unnecessary to postulate a decrease in vascularity in the central portion of the tumor as the only factor involved in the central necrosis which is encountered so frequently in clinical tumors.

#### SUMMARY AND CONCLUSIONS

Prolonged complete arrest of the circulation in a tumor-bearing extremity causes extensive necrosis of chemically induced rat sarcoma. When the circulation to the extremity is arrested up to the limit of subsequent survival of the animal, some viable tumor cells persist. Normal tissues are more resistant than sarcomatous tissues to arrest of blood flow.

Complete arrest of the circulation produces marked central necrosis in the tumor, while the peripheral cells remain viable.

These experiments suggest that hopes of effecting a long range cure of cancer based on the differential sensitivity of tumor cells and normal cells to the arrest of circulation may be ill founded. On the other hand, further investigation of the susceptibility of other types of tumor to arrest of blood flow may conceivably lead to results of practical therapeutic value.

# GANGRENE FOLLOWING DIGITAL NERVE BLOCK ANESTHESIA

REPORT OF A CASE

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NEW YORK

Among the commonest of the so-called bread and butter surgical procedures are minor operations on the fingers and toes under regional anesthesia produced by blocking the digital nerves at the base of the digit. As commonly employed the technic involves the injection of a 0.5 to 2 per cent solution of freshly prepared procaine hydrochloride (with or without a small amount of epinephrine added) into the base of the proximal phalanx either by circular infiltration or by deposition of the anesthetic in the region of the lateral digital nerves. It has been generally recommended that a tourniquet be applied at the base of the digit in order to delay absorption of the procaine into the general circulation, thus enhancing its local effect.

Garlock, in pointing out that this widely followed procedure is not entirely without danger and that gangrene of the involved digit may supervene, attributed this complication to the use of the tourniquet. In the case about to be reported, however, gangrene followed a nerve block anesthesia with which no tourniquet had been used. It was this circumstance which led to a reexamination of the entire problem with a view toward determining the factors to which this unusual complication may truly be attributed.

## REPORT OF CASE

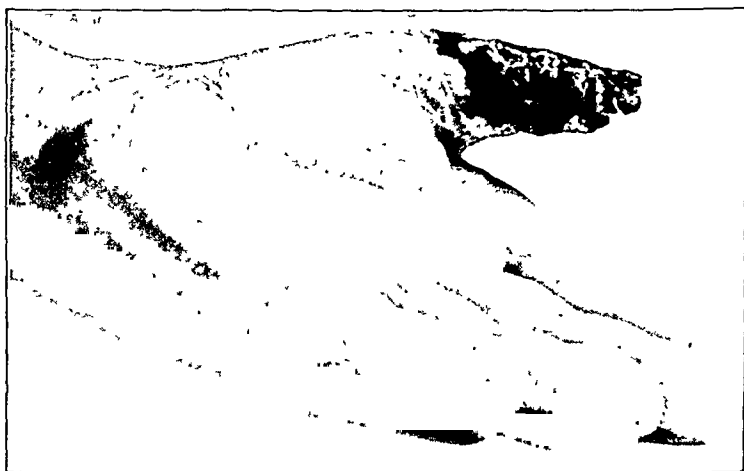
C. S., a 43 year old woman, suffered a minor scratch on her left thumb, followed a few days later by throbbing pain in the tip of the thumb heralding the onset of a felon. This was treated for several days by hot soaks, with no relief. Finally it was incised by her physician with the region under nerve block anesthesia induced by injection of 2 cc. of a 2 per cent procaine hydrochloride solution containing epinephrine hydrochloride into each side of the base of the thumb. A tourniquet was not used. Pus was obtained on incision. Although blanching of the digit occurred, a free flow of blood was noted at the time. Warm boric acid soaks were advised for the postoperative period. On returning home the patient prepared a solution of boric acid with boiling water and immersed her thumb in it. Apparently the anesthesia was still effective, because she expe-

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From the Surgical Service of Dr. Jacob Cohen, Bronx Hospital.

rienced no discomfort until some of the solution reached her palm, whereupon she felt the burn and withdrew the thumb. The next day she began to experience severe pain in the thumb, which took on a dusky hue. Three days later she was admitted to the hospital with a swollen, gangrenous thumb emitting a foul odor. The overlying skin was loose and crepitating. The clinical appearance was similar to that of a *Clostridium welchii* infection, although cultures for this organism were negative. The skin was peeled off in one piece, revealing mottled black underlying tissue, cold and insensitive to pinprick. Enlargement of the original felon incision produced a thin discharge containing *Staphylococcus aureus*, but there was no bleeding. There were no gross evidences of lymphangitis or lymphadenitis.

The urine contained no dextrose, albumin or formed elements. The leukocyte count was 10,500 per cubic millimeter, with 68 per cent polymorphonuclear cells, 3 per cent band cells, 27 per cent lymphocytes and 2 per cent mononuclear cells



Gangrene following digital nerve block anesthesia.

on differential smear. The Wassermann and Kahn reactions of the blood were negative. The value for blood dextrose was 113.7 mg., that for urea nitrogen 12.8 mg., that for uric acid 3.6 mg. and that for creatinine 1.3 mg. per hundred cubic centimeters. Roentgen examination of the thumb showed no evidence of osseous involvement.

The patient was treated conservatively and within a week the mottled areas coalesced, forming a definite line of demarcation running obliquely around the thumb from the base of the metacarpal bone on the radial side to the level of the middle of the proximal phalanx on the ulnar side. This line roughly corresponded with the portion of the thumb which had been exposed by the patient to boiling water. Subsequently it became evident that the proximal part of the involved area had sustained only a third degree burn, while the distal part, including the terminal phalanx and an undetermined portion of the proximal phalanx, had undergone complete necrosis. Accordingly the terminal phalanx was disarticulated and a spontaneous amputation permitted to occur in the proximal phalanx. This was done rather than a primary amputation of both phalanges in

order to permit the retention of even a small fraction of the opposable digit for a better functional result.

Intracutaneous tests for sensitivity to 2 per cent procaine hydrochloride and 1:1,000 epinephrine hydrochloride gave negative results.

It is indeed strange that gangrene following digital nerve block has received so little attention in the American literature. Except in Garlock's report it has not even been recognized here. A survey of the European literature, however, uncovered 25 cases published in greater or lesser detail. I have summarized them in tabular form so that common factors may become evident. Many of the data as published are incomplete, and one must be on guard against unwarranted assumptions. In one case report, for example, reference was made to the use of procaine hydrochloride solution for a block anesthesia without any mention of epinephrine. A personal check-up revealed that in this particular case epinephrine was actually used but not mentioned in the report, the author apparently not having considered its use of sufficient significance at the time to mention it. Unless the use of epinephrine is specifically denied one cannot assume that the substance was not used as a matter of routine. Similar confusion obtains at times concerning the use of a tourniquet and other points of technic. I have tried to include only those factors definitely indicated in the reports.

#### ETIOLOGY

A glance at the accompanying table will suffice to show that age and sex do not appear to play decisive roles in this condition. In no case was syphilis, diabetes or any other constitutional disease demonstrated; so one looks rather to local factors for the causation. A wide variety of initial pathologic conditions is presented, many (but not all) representing infections. In only 1 case (case 10) was there evidence of preexisting vascular involvement. The anesthetic agents used include cocaine hydrochloride; beta eucaine (benzoylvinyldiacetone-alkamine hydrochloride); sterile water and procaine hydrochloride in varying concentrations and in amounts varying from 1.5 to 30 cc.

It has been suggested that the anesthetic agent may have been chemically altered by age, light or some other factor in such a way as to make it toxic. This is contraverted by the fact that several authors, notably Rupp and Kirchbach, prepared the solution from tablets immediately before use. Makai, with this in mind, subjected his suspected procaine-epinephrine solution to qualitative and quantitative analysis, with negative results. The solution used in the case reported here was used for other patients with no untoward effects. Siebert reported a similar experience.

In order to determine whether allergy to procaine was a factor, an intradermal injection of procaine hydrochloride was performed on our

# Summary of Reported Cases

Case	Author	Patient's Sex	Patient's Age	Initial Condition	Operation	Anesthesia	Epinephrine	Tourniquet	Extent of Gangrene	Comment
1	Strauss.....	..	14	Ingrown toe nail	Removal of nail section	30% cocaine hydrochloride at base and under nail	..	..	Entire digit	
2	Marinowski.....	F	19	Paronychia	Incision and drainage	1.5 cc. 10% beta eucaine * at level of second phalanx	..	0	Distal two phalanges	
3	Siebert.....	F	39	Infected puncture wound	Incision and drainage	0.5% cocaine hydrochloride and eucaine at base	0	+	Entire digit	
4	Siebert.....	F	50	Embedded needle fragment	Removal of needle	0.5% cocaine and eucaine at base	0	..	Distal two phalanges	
5	Dejardin.....	F	22	Paronychia	Incision and drainage	1% cocaine hydrochloride at base	..	..	Entire digit	
6	Dejardin.....	F	23	Talon	Incision and drainage	Tepid sterile water at base	..	..	Entire digit	
7	Dejardin.....	M	34	Traumatic amputation of phalanx	Disarticulation of terminal phalanx	1% procaine hydrochloride at base	..	..	Entire digit	
8	Chevrier.....	..	..	Severed extensor tendon	Tendon suture	Procaine hydrochloride at base	+	..	Terminal phalanx	
9	Dinanian.....	M	40	Ingrown toe nail	Removal of nail	0.5% procaine hydrochloride at base	+	..	Entire toe and metatarsal bone	Only case in which gangrene extended proximal to site of injection of anesthetic
10	Toupet.....	..	..	Trophic disturbance of nail following freezing of foot	.....	0.5% procaine hydrochloride at base	+	..	Entire toe	Probable previous vascular involvement
11	Moulouquet.....	F	40	Embedded needle fragment	Removal of needle	3.4 cc. 0.5% procaine hydrochloride at base	0	0	Entire digit	
12	Halla.....	F	..	Paronychia	Incision and drainage	1.2 cc. 2% procaine hydrochloride at base	+	0	Most of finger	Anesthetized finger soaked in boiling water
13	Wolfsohn.....	..	..	.....	.....	8-10 cc. procaine hydrochloride at base of terminal phalanx	+	..	Terminal phalanx	
14	Costantini and others	..	..	.....	.....	Cocaine hydrochloride .....	+	..	Entire digit	
15	Costantini and others	..	..	.....	.....	Cocaine hydrochloride .....	+	..	Entire digit	



16	Garlock	M	45	Imbedded needle fragment	Removal of needle	Procaine hydrochloride at base	..	+	Half of thumb	
17	Garlock	F	29	Paronychia	Incision and drainage	1% procaine hydrochloride at base	..	+	Distal two phalanges	
18	Garlock	..	29	Talon	Incision and drainage	1% procaine hydrochloride at base	..	+	Terminal phalanx	Tourniquet applied 1 hour
19	Garlock	M	22	Imbedded needle fragment	Removal of needle	6 cc. 1% procaine hydrochloride at base	+	+	Small slough at level of terminal phalanx	Treatment started 3½ hours post-operatively
20	Mukul	M	47	Paronychia	Removal of nail	1.5-2 cc. 1% procaine hydrochloride at base	+	..	Small slough at site of injection	
21	Mukul	F	..	Ingrown toe nail	Hemisection of nail	2-3 cc. 1% procaine hydrochloride at base	+	..	Tip of toe	
22	Hickok	F	29	Melanoma of great toe	Excision of tumor	25-30 cc. 0.5% procaine hydrochloride in intermetatarsal space	+	0	None	Treatment started 2 hours post-operatively
23	Kochanharoff	M	60	Splinter under nail of finger	Removal of splinter	5 cc. 0.5% procaine hydrochloride at base	+	..	Entire digit	
24	Kirchbach	M	27	Ingrown toe nail	Removal of nail	8 cc. 0.25% procaine hydrochloride injected at different levels	+	..	Almost entire digit	
25	Rupp	F	23	Paronychia	Incision and drainage	10-15 cc. 0.5% procaine hydrochloride at base of digit	+	..	Dorsum of terminal phalanx	
26	Rupp	..	..	Ingrown toe nail	Removal of nail and sequester-tomy	5-8 cc. 1% procaine hydrochloride at base	0	..	Down to level of injection	
27	DeKoffe	F	11	Chronic osteitis of terminal phalanx	Removal of foreign body	3 cc. 2% procaine hydrochloride at level of second phalanx	+	+	Down to level of proximal injection	
28	Lambert and others...	M	28	Imbedded foreign body; paronychia	Incision and drainage	2.5 cc. 2% procaine hydrochloride at proximal interphalangeal joint medially and distal joint laterally	+	0	Almost entire digit	Anesthetized finger soaked in boiling water
29	Lambert and others...	F	24	Paronychia	Incision and drainage	4 cc. 2% procaine hydrochloride at base	+	+		
30	Kaufman	..	13	Talon	Incision and drainage		+	+		

patient. No abnormal local or general reaction resulted. This is supported by Garlock's statement that 3 of his 4 patients had had previous injections of procaine hydrochloride without ill effects.

The role played by epinephrine is not readily discerned. Since its use as a synergist in the induction of local anesthesia was first advised by Braun it has gained wide acceptance. Neugebauer first cautioned against its use in high concentrations, but it is still commonly employed in very weak solutions. Instances of gangrene of the abdominal wall (Gebele; Koch) and of the scrotum (de Smeth) following the use of dilute procaine-epinephrine solutions have been reported; such gangrene is generally attributed to the epinephrine. Of 20 cases in this series, epinephrine was used in 15. Intracutaneous tests for sensitivity to epinephrine were carried out by Makai and in my case in order to determine whether allergy to this substance might be a factor in the causation of the gangrene. In both instances the cutaneous tests gave negative results. Such tests do not entirely exclude this possibility, however, and in reading the original case reports one is struck by the frequency with which an unusual and prolonged blanching of the digit was noted after the injection of the epinephrinized solution. Notwithstanding this suggestive evidence, it must not be forgotten that in at least 4 cases the injected material contained no epinephrine.

The tourniquet as a contributory factor is likewise subject only to partial indictment. Garlock considered it a major factor because it was used in all 4 of his cases, but a review of the literature reveals that of the 8 other cases in which the use of a tourniquet was definitely discussed it was employed in only 2. It appears reasonable to suppose, however, that a tight tourniquet may contribute to local vascular injury, and I personally feel that it should be counted a contributory factor in those cases in which it was used. In any event, by retarding absorption of the injected material into the general circulation, it enhances whatever pathogenic properties may be inherent in the injected solution.

A word or two should be added about the danger of hot soaks immediately after an operation under nerve block anesthesia. In my own case, as well as in that reported by Halla, a severe burn was caused by the patient's immersion of the anesthetized digit in boiling water. It is possible that this may have occurred in other cases in this series without even coming to the attention of the respective authors. If the universally discredited phenol dressing can result in gangrene, then certainly boiling water can easily do the same.

#### PATHOGENESIS

One observation stands out clearly in all the cases in the series: The extent of the gangrene is uniformly limited proximally by the

level of the injection. In only 1 case (case 9) did the tissue proximal to that line become involved, and even in that case the proximal extension was progressive, inflammatory and slowly advancing, unlike the usual early demarcation seen in the other cases.

Prompt and clearly defined demarcation of a lesion signifies vascular involvement primarily; so it must be assumed that the essential lesion in these cases is closure of the arterial supply. Venous involvement and lymphatic involvement may coexist, but either or both of these factors would be insufficient to produce dry gangrene unless accompanied by arterial closure. Lambert and Snyers have suggested that an initial thrombophlebitis occurs with a later retrograde thrombosis of the arterial supply via the capillaries. I find this process difficult to visualize, and I do not see that it explains adequately the failure of such a retrograde arterial thrombosis to extend proximal to the level of the injection. It seems more likely that a direct primary injury to the arteries occurs at the level of the injection, with simultaneous or subsequent involvement of the veins. The dark color assumed by the affected digit was said by Lambert and Snyers to be evidence of primary venous rather than arterial thrombosis, but it is well known that arterial occlusion alone, such as that occurring in the presence of embolism, can often produce a cyanotic rather than a blanched reaction in the infarcted area.

That the closure of the arterial blood supply is not immediate is attested by the frequently mentioned observation that during the operation performed after the institution of the nerve block free bleeding was observed. It is only after the gangrenous process has already begun, hours or days later, that incision no longer produces bleeding. This lag factor would seem to indicate that some circumstance in the nerve block produces injury to the digital vessels, which in turn initiates a train of events leading to progressive local thrombosis and, if sufficiently marked, to arterial occlusion. The blood supply of the digits being terminal, this can lead only to ischemic gangrene. Such a postulation would explain why gangrene occurs only distal to the site of the injection.

The exact nature of the factor producing the local vascular injury is not yet entirely clear. That the tourniquet and the epinephrine may be factors has already been indicated. Direct pressure by the mass of the injected material may play a role in view of the lack of tissue distensibility at the base of the digits. Minute quantities of protoplasmic poisons derived from chemical changes in the anesthetic drugs must also be considered, as well as a peculiar local allergic response. Susceptibility to vascular thrombosis may be increased by the slowing of the blood stream attendant on a local inflammatory lesion or perivascular lymph-

angitis. It would appear that any one of the factors mentioned may be absent in any given case but that others may compensate for it and combine in such a way as to produce a state favorable to thrombosis.

#### TREATMENT

In only a few of the recorded cases did the patient apply for treatment before an obviously irreversible process had occurred. Koschucharoff was able to begin treatment only two hours after the operation, when his attention was called to the blanching, pain and stiffness of the involved finger. He immediately instituted massage, movement and warm soaks, with the result that the circulation was restored and gangrene avoided. Heinicke advised that a pancreatic extract (padutin) be administered in the hope of relieving arterial spasm.

After gangrene has become inevitable one should be guided by general surgical principles. It is advisable to wait for a well defined line of demarcation, and the choice between operative and spontaneous amputation can be made on the basis of functional and plastic considerations.

#### PROPHYLAXIS

Until a fuller understanding of the cause of gangrene following nerve block is achieved, one cannot offer a technic which is entirely safe. On the basis of present knowledge, however, the following precautions seem advisable:

Digital nerve block is contraindicated in all cases in which there is preexisting vascular disease.

A contraindication likewise exists in the presence of any inflammatory process or lymphatic involvement at the projected site of the block.

The use of a tourniquet is not advisable. If a bloodless field is desired an Esmarch bandage is to be preferred. If a tourniquet is to be used it should be applied at a level other than that used for the nerve block, so as to avoid double trauma to the digital vessels at the same site. After removal of the tourniquet the indented tissues should be massaged in such a way as to aid in the reestablishment of circulation. If the projected operation is of long duration and the tourniquet is desired in order to prolong the anesthesia, it would be preferable to use another type of anesthesia altogether.

The use of epinephrine should be avoided in digital nerve block procedures. With procaine hydrochloride alone anesthesia can be effected which, although of shorter duration, is satisfactory. Moure and Momburg strictly prohibited the use of solutions containing epinephrine in operations on the finger, toe and penis.

Small quantities of fluid should be injected directly over the lateral digital nerves rather than a large volume of fluid that will completely encircle the base of the finger and produce blanching of the tissues by local pressure. Where feasible, the lateral injections should be made at different levels in order to avoid too great a distention of tissues at one level. De Rougemont has advised that the block be performed in the interdigital space opposite the heads of the metacarpal bones. The tissues are more distensible here and permit injection of a larger amount of anesthetic fluid.

After completion of the operative procedure it is wise to massage the site of the injected fluid in order to promote its prompt absorption and to reduce pressure on the vessels.

Makai has advised that all patients who have been subjected to nerve block anesthesia be seen again one hour after the operation in order to determine whether the circulation is adequate. This may permit active therapy before irreversible changes have occurred.

Patients should be cautioned about the use of hot soaks in the immediate postoperative period. They should be told to try out the temperature of the solution with the hand which was not operated on so that burns of the anesthetized digits can be avoided.

#### SUMMARY

Gangrene is a rare complication of digital nerve block anesthesia.

A case is reported and a review of the literature is presented. The etiology, pathogenesis and treatment are discussed.

The prophylaxis is indicated, with special stress on avoiding the use of epinephrine and the tourniquet.

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# PATHOLOGY OF DEHYDRATION SHOCK

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The dehydration frequently observed in surgical patients may be due to several possible causes acting singly or in combination. Excessive loss of fluid may occur from the upper part of the alimentary tract as the result of vomiting or of drainage from a duodenal, pancreatic, biliary or intestinal fistula. Prolonged gastrointestinal drainage by the Wangenstein or the Miller-Abbott tube has the same effect. Similar loss may take place from the lower part of the alimentary tract in the presence of diarrhea. Excessive perspiration may lead to water depletion in a patient subjected to an operative procedure in an overheated operating room, and the excessive sweating which often accompanies both primary and secondary shock may cause large losses of fluid. Finally, Davidson<sup>1</sup> and Underhill and his associates<sup>2</sup> have called attention to the water which may evaporate from a traumatized surface in an extensive burn.

The significance of dehydration lies in the circumstance that it is capable, in itself, of producing circulatory failure (Davis<sup>3</sup>) in combination with changes which are frequently considered to result from the presence of some toxic factor (Moon<sup>4</sup>). The following case report is typical:

A Negro 42 years of age was admitted to the Charity Hospital of Louisiana at New Orleans suffering from intestinal obstruction. Vomiting had been frequent and severe, and at the time of admission the patient was dehydrated and appeared to be in a state of circulatory failure. The extremities were cold, and the superficial veins were empty and collapsed. The temperature was 98 F., the pulse rate 120 per minute and the systolic pressure 75 mm. of mercury; the diastolic pressure could not be obtained. The patient died four hours after entering the hospital.

Postmortem examination revealed that 28 cm. of the jejunum had been strangulated by adhesions and was edematous and dark red, with evidence of early

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gangrene. The peritoneal cavity contained 500 cc. of serohemorrhagic fluid. The pleural cavities were dry. The lungs were heavy and moist, and numerous petechial hemorrhages were present beneath the visceral pleura. All the other viscera were reduced in weight. The spleen, which was contracted, weighed 65 Gm.

Microscopic examination revealed marked distention of the alveolar capillaries, which were filled with closely packed red blood cells. The alveolar spaces were filled with fluid, and extravasations of blood were present in many areas. Examination of the liver revealed considerable distention of the capillaries in the region of the central veins of the lobules.

These observations are frequent in cases of intestinal obstruction with strangulation, and they have been advanced, as has been pointed out, to support the theory of a toxic factor. A similar picture, however, is observed with other conditions, such as burns, with which circulatory failure associated with hemoconcentration is present. In this paper an attempt will be made to demonstrate that they may be reproduced by the simple withdrawal of water from the blood and the tissue spaces (Davis<sup>5</sup>).

#### MATERIALS AND METHODS

Seventeen dogs were used for the experimental studies and 6 for the control studies. All weighed from 5 to 10 Kg. After the dogs had been anesthetized by the intravenous injection of pentobarbital sodium ( $\frac{1}{4}$  grain [15 mg.] per kilogram of body weight), sodium chloride solution (25 per cent) was injected subcutaneously into a hindleg of each animal in doses of 25 cc. per kilogram of body weight. Marked edema occurred at the site of injection, and two or three hours after the solution had been introduced the blood pressure began to fall. As the local edema increased, the fall in blood pressure became more pronounced, and death usually occurred within five to ten hours after the injection. The hemoconcentration and other physiologic changes associated with this form of circulatory failure have been described elsewhere (Davis<sup>6</sup>).

The animals were examined immediately after death. The organs were examined grossly, then removed and immediately placed in a 10 per cent concentration of solution of formaldehyde U. S. P. or, if glycogen stains were to be made, in absolute alcohol. The tissues, after proper fixation, were embedded in celloidin (a pyroxylin preparation) and were stained with hematoxylin and eosin or, in several instances, with Best's carmine stain for glycogen and with scarlet red stain for fat.

#### TISSUE CHANGES

*Site of Injection.*—Marked edema of the subcutaneous and intramuscular tissues was present at the site of injection. The fluid was usually colorless but occasionally pink as the result of hemolysis of the contained blood. The veins in the subcutaneous tissues showed evidence of recent thrombosis. The muscular tissue

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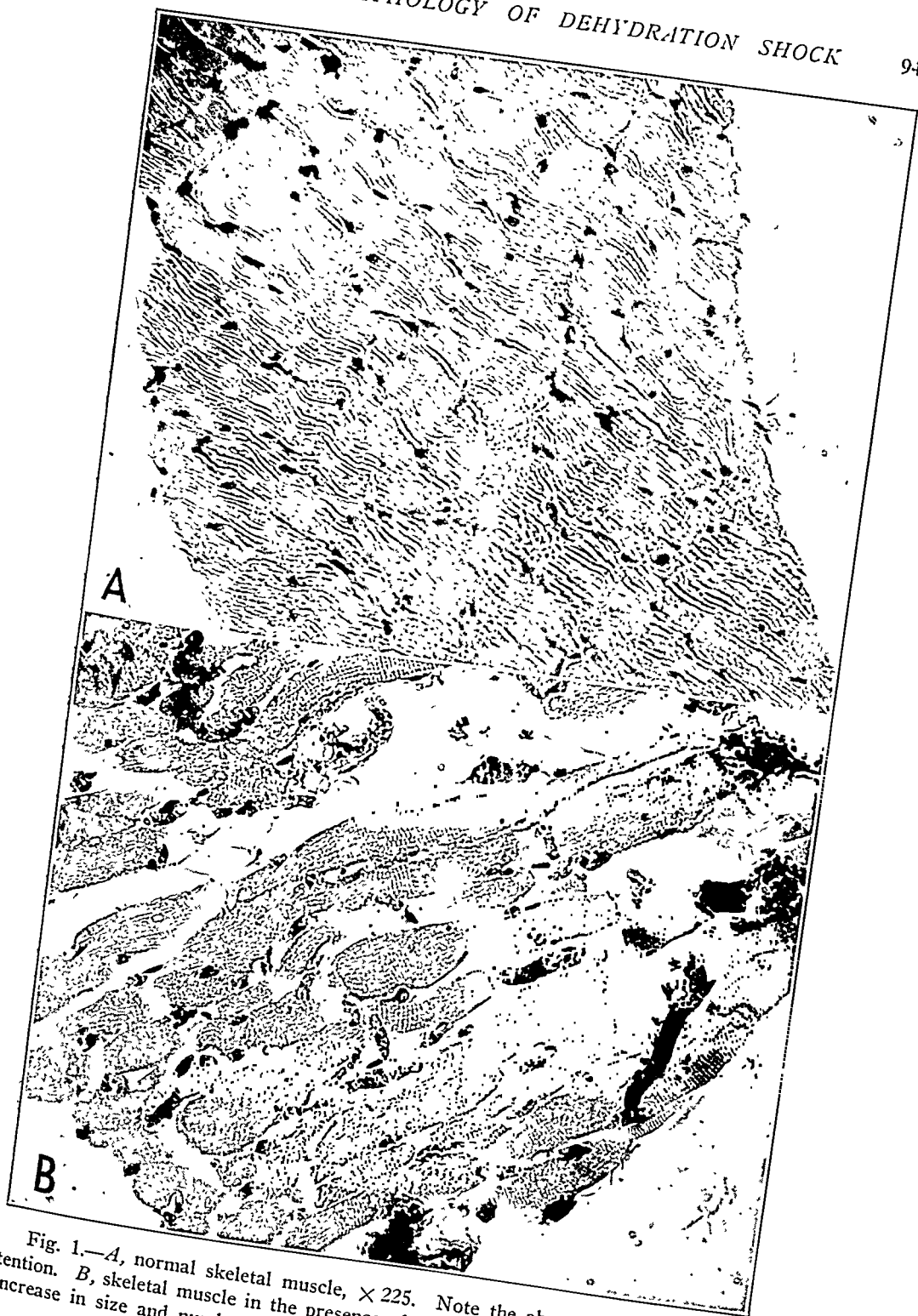


Fig. 1.—*A*, normal skeletal muscle,  $\times 225$ . Note the absence of capillary distention. *B*, skeletal muscle in the presence of dehydration shock,  $\times 225$ . Note the increase in size and number of open capillaries.

was pale and edematous. Microscopic examination confirmed the presence of edema of the subcutaneous tissues and revealed fluid between many of the muscle fibers.

The subcutaneous tissues elsewhere in the body were dry and sticky. The muscular tissues were also dry and were rather pale on inspection, though section resulted in the oozing of dark blood. Microscopic examination of the muscles revealed marked distention of the capillaries, which were filled with red blood cells in dense masses (fig. 1). There was an increase, by actual count, in the number of open capillaries in the muscular tissues. No parenchymatous changes were noted.

*Cardiovascular System.*—The heart showed a marked degree of contraction. The left ventricle was empty in most of the animals, but the right auricle and ventricle were usually filled with thick, partly coagulated blood. The pericardial sac usually was dry in appearance and contained no fluid. Small hemorrhages were frequently observed in the subepicardium, in the neighborhood of the coronary vessels. Both large and small hemorrhages were observed beneath the endocardium of the right ventricle and, perhaps more often, of the left ventricle. They extended from the endocardium into the chordae tendineae (fig. 2). Subendocardial hemorrhages were also seen in both the left and the right auricle and in the auricular appendages. The myocardium was somewhat cyanotic, and the superficial veins were distended with blood.

Microscopic examination revealed the subepicardial and subendocardial hemorrhages already described (fig. 2). They were recent and showed no evidences of neighboring tissue reaction in the form of leukocytic infiltration. The overlying endocardium and pericardium appeared intact. The source of the hemorrhages was found in the capillaries of the underlying myocardium. These, by actual count, were increased in number and were considerably distended with closely packed red blood cells. In many instances the capillaries had ruptured, permitting the escape of red blood cells between the fibers of the myocardium and beneath the endocardium and the epicardium. The myocardial fibers showed no evidences of fragmentation or of other parenchymatous changes. The arteries showed a relative absence of blood. The inferior and superior venae cavae and the tributary veins were somewhat empty in appearance, and the blood contained in them was thick and viscous.

*Respiratory System.*—The pleural cavities contained no fluid, and the surfaces were sticky and dull looking. The lungs were brick red except for certain areas, particularly at the bases, which were purple-red. Numerous petechial hemorrhages were seen beneath the visceral pleurae (fig. 3). They were most frequently present at the bases and toward the hili of the lungs and varied in size, some being the size of a pinpoint and others considerably larger. The cut surfaces of the lungs exuded dark blood which resembled venous blood. The lungs contained air, but occasional firm nodules of pulmonary tissue were the sites of hemorrhage or edema. The mucous membranes of the trachea and bronchi were reddened, and not infrequently blood-stained mucus was found on the surfaces. The pulmonary artery and vein usually contained inspissated dark red blood.

Microscopic examination confirmed the presence of hemorrhage beneath the visceral pleura. The alveolar capillaries were markedly distended with closely packed red blood cells, large numbers of which were found in the alveolar spaces as the result of numerous capillary ruptures. The capillaries in the walls of the bronchi and bronchial mucosa were greatly distended with red blood cells. Focal areas of pulmonary edema were seen, in which the alveolar spaces were filled with

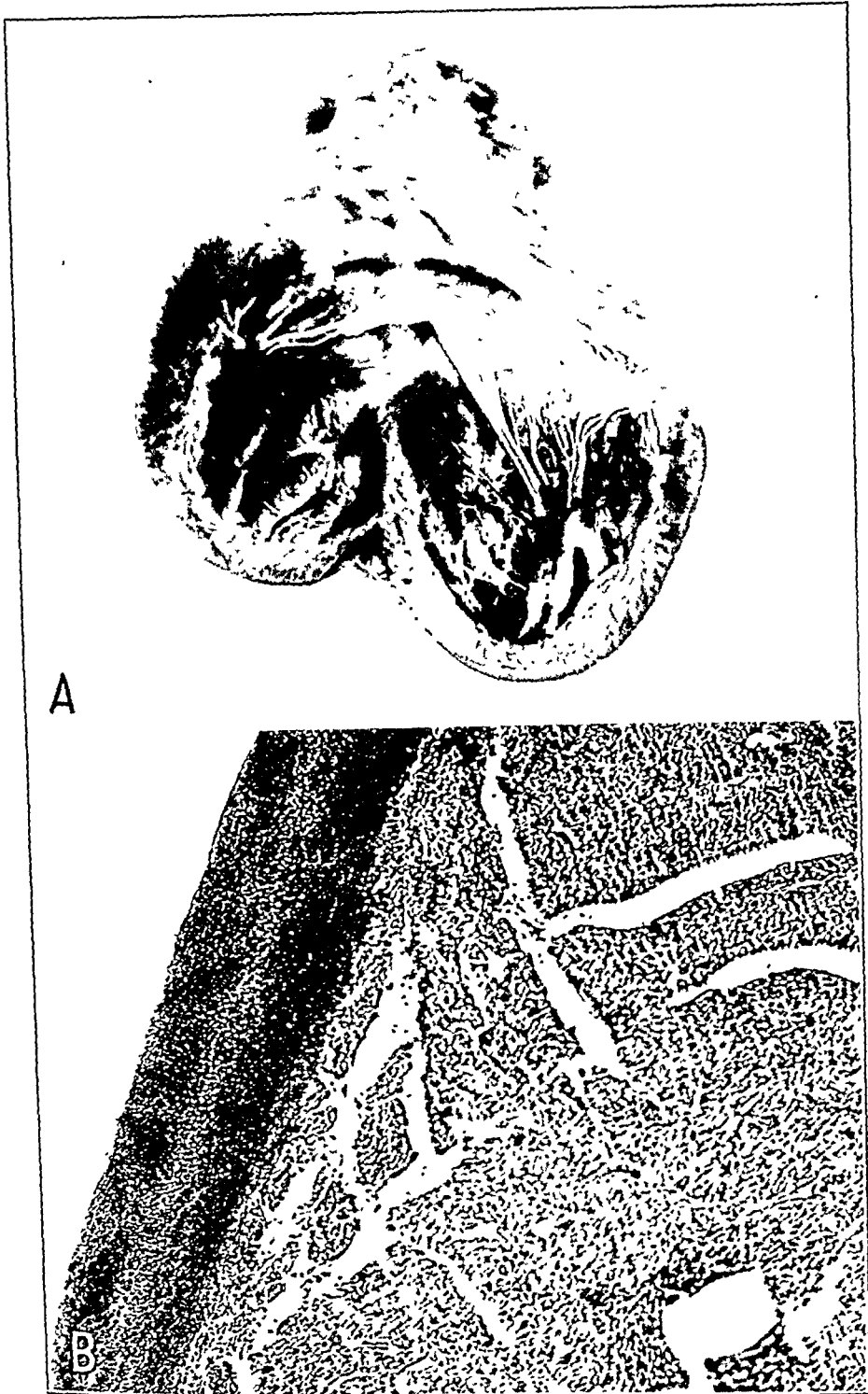


Fig. 2.—*A*, heart (gross specimen). Note the hemorrhage beneath the endocardium. *B*, heart,  $\times 170$ . Note the hemorrhage beneath the endocardium.

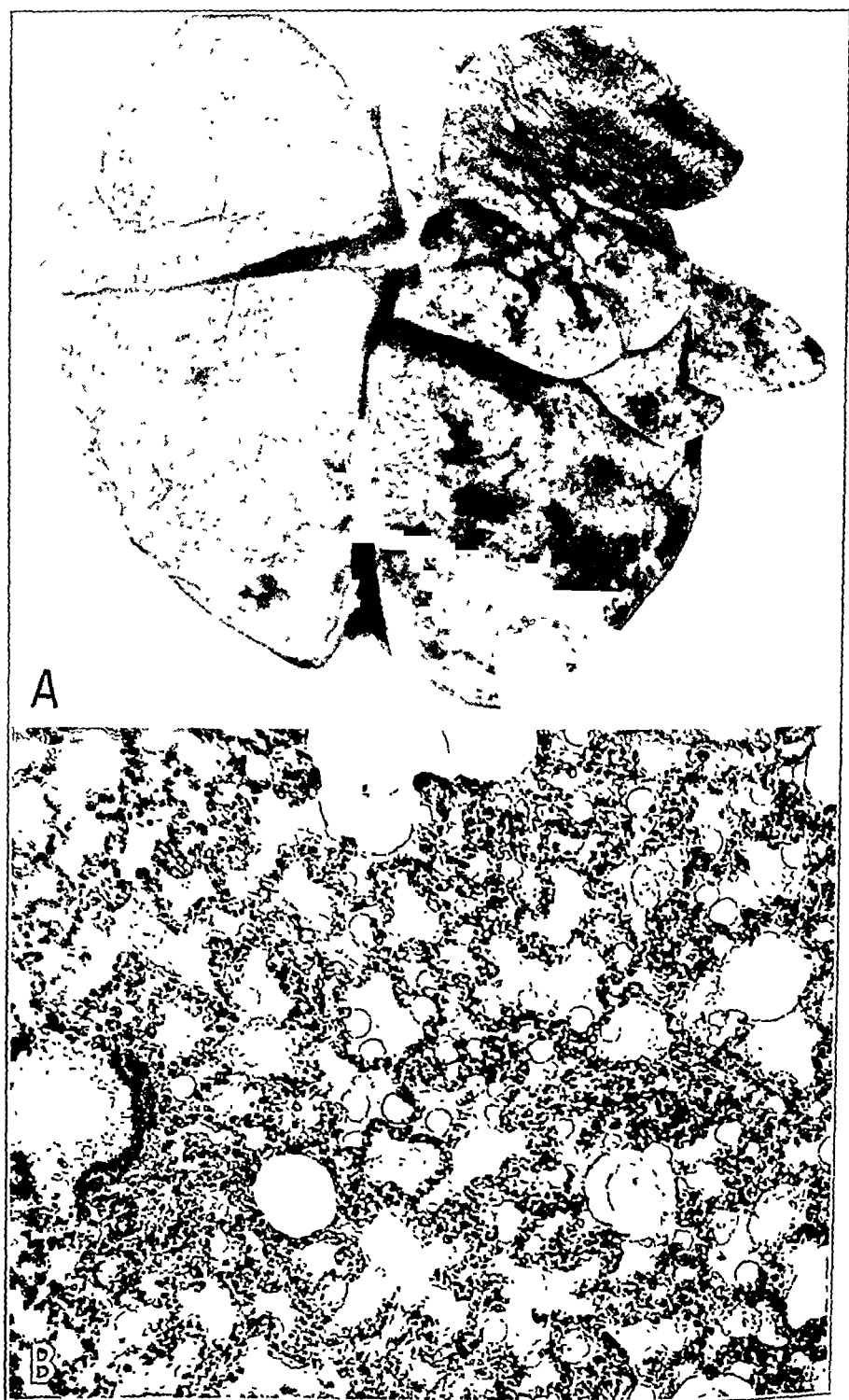


Fig. 3.—*A*, lung (gross specimen). Note the subpleural hemorrhages. *B*, lung,  $\times 170$ . Note the distention of the alveolar capillaries and the edema fluid in the alveolar spaces.

a clear, acellular fluid (fig. 3). The extent of the pulmonary edema could be correlated with the duration of the shock; the animals which died rapidly showed little or no pulmonary edema, but in those in which the low blood pressure had existed for longer periods prior to death the edema was considerably more extensive. In a few animals large, pale macrophages were seen in the alveoli.



Fig. 4.—*A*, stomach and duodenum (gross specimen). There is congestion of the mucosal blood vessels. *B*, same,  $\times 170$ . Note the distention of the mucosal capillaries.

*Alimentary Tract.*—The peritoneal cavity contained no fluid. The parietal peritoneum was diffusely reddened as the result of distention of the capillaries, and similar, more marked changes were observed in the visceral peritoneum. The omentum was dry and sticky, and the omental vessels showed a moderate degree of dilatation.

The mucous membrane of the esophagus was moderately reddened, but no evidences of ulceration or petechial hemorrhages were noted. The stomach, in addition to distention of the serosal vessels, showed diffuse reddening of the mucous membrane, particularly in the pyloric region, but no evidences of gastric ulceration or of hemorrhages into the mucous membrane. Microscopic examination revealed a considerable degree of distention of the capillaries, particularly in the gastric mucosa and serosa.

The mucosa of the small intestine was extremely reddened (fig. 4), particularly in the duodenum and the upper part of the jejunum. The change gradually diminished in intensity throughout the remainder of the small intestine. Blood-stained secretion was frequently found on the mucosal surfaces. Microscopic examination revealed capillary congestion throughout the wall of the duodenum; it was most noticeable in the capillaries of the mucosa (fig. 4). There was no evidence of ulceration of the mucosa.

The changes in the large intestine were not constant and consisted merely of congestion of the serosal and mucosal capillaries. They were most evident in the left half of the colon. Blood-stained material was frequently found on the mucosal surfaces. No ulceration was noted.

The liver was usually somewhat smaller than normal and was reddish black. Occasional petechial hemorrhages could be seen beneath the hepatic capsule. Dark blood, resembling venous blood, oozed from the cut surfaces. Microscopic examination revealed marked capillary distention throughout the organ, most noticeable in the capillaries around the central vein. The hepatic cells revealed a moderate degree of hydropic degeneration. Extravasated blood was frequently observed among the liver cells and beneath the capsule, the extravasations occasionally being associated with focal areas of liver cell necrosis. In several animals the liver cells presented an empty appearance, particularly in the midzonal and periportal areas of the liver lobules. The nuclei in these cells were situated in their normal positions, and it was assumed that the empty appearance was not due to fatty changes. Stains for fat verified the absence of fatty metamorphosis, and stains for glycogen revealed that the cells were depleted of their normal glycogen content (fig. 5). The significance and the mechanism of production of these hepatic changes will be discussed later.

Examination of the spleen revealed a constant reduction in weight and size. The decrease in size varied according to the duration of life after the injection, the organ being extremely contracted and small in those animals which had survived for the longest periods. In most animals varying numbers of petechial hemorrhages were found beneath the capsule (fig. 6). The hemorrhages varied in size, some being large. The cut surface of the spleen had a rather dry appearance.

Microscopic examination usually showed marked distention of the splenic vessels, which were closely packed with red blood cells. Extravasations of blood were frequent, occurring most often into the malpighian nodules and the splenic parenchyma subjacent to the capsule (fig. 6). The extravasations were evidently recent, since no evidence of inflammation was observed in the vicinity.

*Urinary System.*—Examination of the kidneys revealed a considerable degree of distention of the capsular capillaries. On section the renal parenchyma had a cyanotic appearance. Microscopic examination showed a rather marked degree of congestion of the glomerular and intertubular capillaries. In occasional animals a considerable degree of parenchymatous degeneration was observed in the tubular epithelium. Congestion of the capillary vessels was the only change observed in the ureters and urinary bladder.

*Endocrine System.*—Of the endocrine glands, only the pancreas and the thyroid and adrenal glands showed notable changes. The pancreas revealed only congestion of the capillary blood vessels. The pituitary gland exhibited an extreme degree of distention of the capillary blood vessels, particularly in the anterior lobe. In occasional animals small extravasations of blood were found among the



Fig. 5.—Liver,  $\times 170$ . There is glycogen depletion of the hepatic cells in the periportal and midzonal regions; note the "empty" appearance of the cells.

cells of the anterior lobe. The cytoplasm of many of these cells had a granular appearance, suggestive of some degree of parenchymatous degeneration. A considerable degree of distention of the capillaries of the thyroid was observed, but the colloid content of the acini was unaltered.

The adrenal glands showed uniform, well marked changes. There was considerable distention of the capillary vessels throughout the gland, most marked in the medulla and in the zona reticularis and zona fasciculata of the cortex.

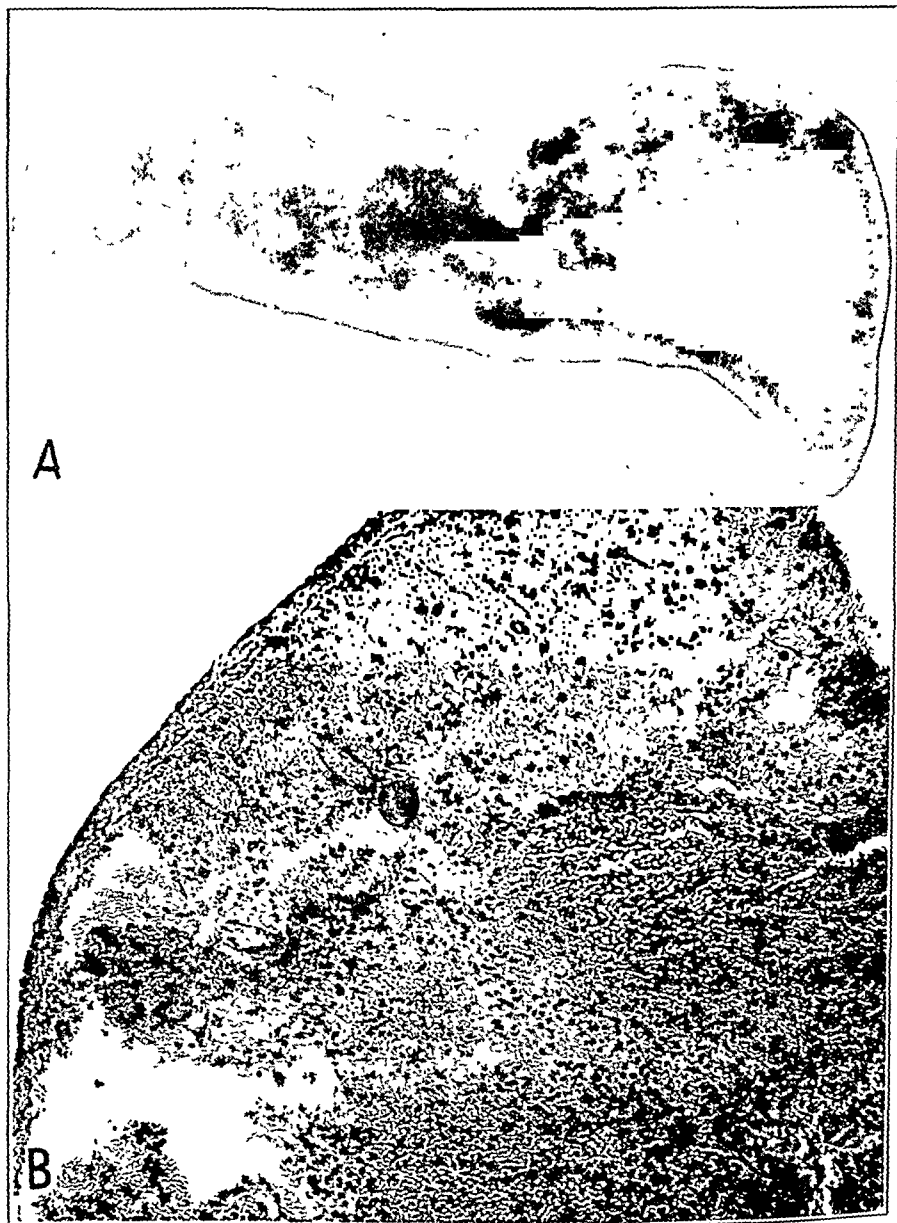


Fig. 6.—*A*, spleen (gross specimen). Note the hemorrhages beneath the splenic capsule. *B*, spleen,  $\times 170$ . Note the hemorrhage beneath the splenic capsule and into the splenic parenchyma.

Diffuse and focal collections of polymorphonuclear leukocytes were observed in this portion of the cortex, the leukocytes being so numerous that an inflammatory process was simulated (fig. 7). Numerous petechial hemorrhages were observed



in both the cortex and the medulla. In addition, focal areas of cell necrosis were observed in the zona fasciculata and the zona reticularis.

*Nervous System.*—Only the brain was examined. The capillaries of the dura presented an extreme degree of congestion when the skull was opened. The cere-



Fig. 7.—Adrenal gland,  $\times 170$ . Note the distention of the capillaries and the infiltration of the zona reticularis and the zona fasciculata by polymorphonuclear leukocytes.

brospinal fluid was scanty, and the brain was somewhat shrunken. In the meninges over the cerebrum, cerebellum, medulla and pons the superficial capillaries were markedly distended, and the entire brain had a flushed, reddish appearance. The larger vessels in the pia-arachnoid were distended with dark blood. Gross petechial hemorrhages of varying sizes were observed in the leptomeninx (fig 8).

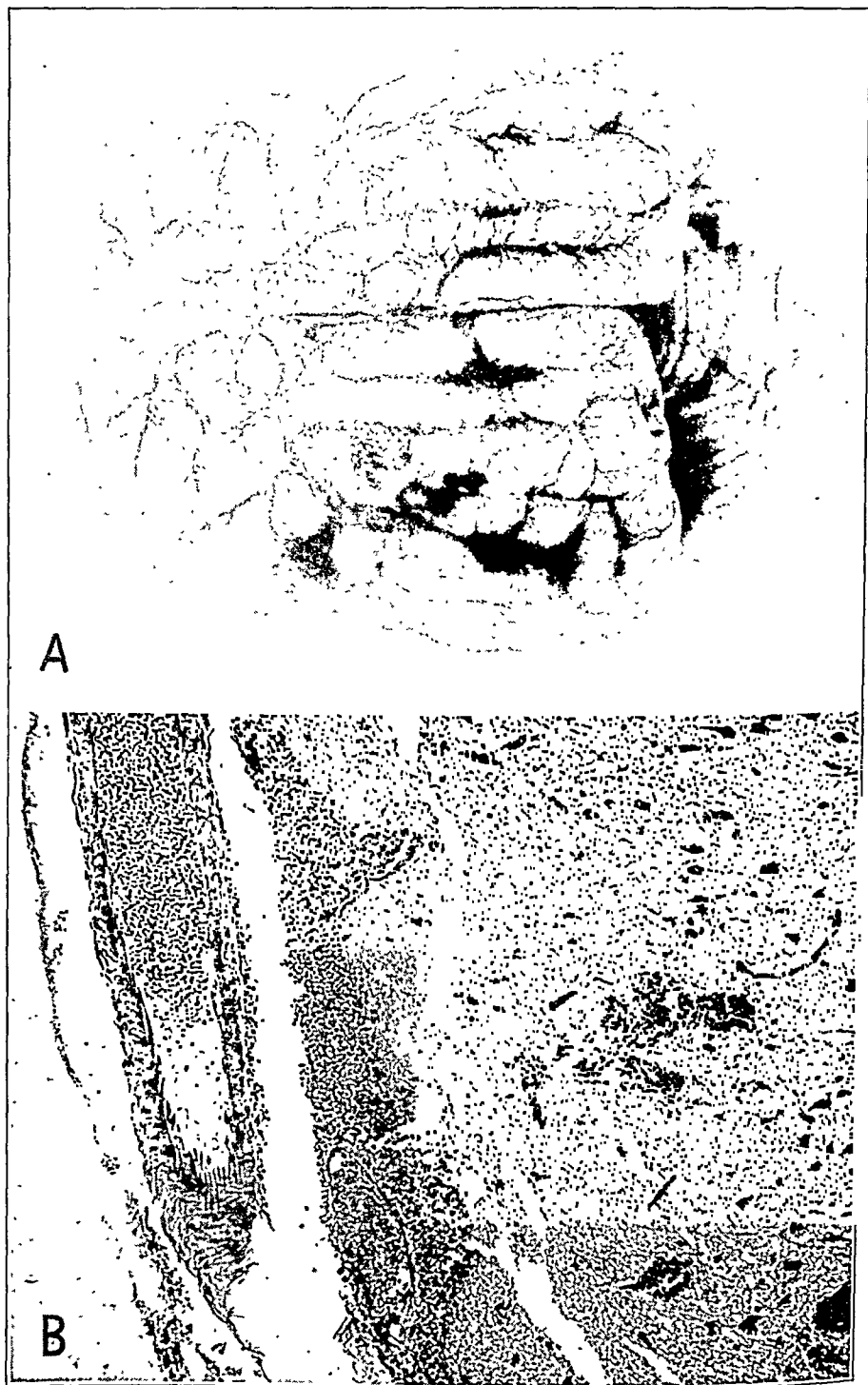


Fig. 8.—*A*, brain (gross specimen). Note the hemorrhages into the leptomeninx and the distention of the capillaries. *B*, brain,  $\times 170$ . Note the hemorrhages into the leptomeninx and underlying cerebral tissue and the distention and increase in number of the open capillaries.

Microscopic examination revealed the capillaries of the brain to be extremely distended with closely packed red blood cells. The number of open capillaries was increased, both by inspection and by actual count. Petechial hemorrhages were observed in the substance of the brain in the neighborhood of the distended blood vessels. The presence of hemorrhage into the leptomeninx was confirmed by microscopic examination (fig. 8). There were no evidences of leukocytic reaction in the vicinity of these hemorrhages. The cells of the nervous system showed a variety of changes, but the significance of the alterations should not be stressed, since postmortem changes occur with great rapidity in tissues of the nervous system.

#### COMMENT

The tissue changes associated with acute loss of body water may be summarized as follows: widespread dilatation of the capillary blood vessels; an increase in the number of open capillaries; petechial hemorrhages beneath the capsules of the liver and spleen and beneath the visceral pleura; petechial hemorrhages into the leptomeninx; similar hemorrhages in the spleen, lungs, myocardium, epicardium, endocardium, brain, liver and adrenal glands; foci of cell necrosis in the adrenal gland, particularly in the cortex, and pulmonary edema, the degree varying directly with the duration of shock.

Similar changes have been described as accompanying other conditions in which hemoconcentration is present. Burns, for instance, produce a pathologic picture resembling in many ways that of dehydration shock. Similar changes associated with shock were produced by Moon and Morgan<sup>7</sup> by the implantation of sterile muscle into the peritoneal cavity of the dog.

Moon, on the basis of this work, stated the belief that a toxic substance is the basic factor in the production of similar lesions of the tissues in cases of clinical shock. The present study, on the other hand, suggests that a reduction of plasma volume by the simple removal of water from the blood and tissues is capable of producing lesions in every way comparable to those described by him. It would seem, therefore, to be unnecessary to postulate the presence of a toxic substance to explain these changes.

The question next arises as to the mechanism of production of the tissue changes described. The most widespread and most obvious is the distention and the increase in number of open capillaries throughout all the tissues. Previous work (Davis<sup>8</sup>) has indicated that the hemoconcentration accompanying dehydration shock is associated with a great diminution of the oxygen content of the blood. The reduction points to the presence of anoxemia, which must have definite effects on the

7. Moon, V. H., and Morgan, D. R.: Experimental Pulmonary Edema, *Arch. Path.* 21:565-577 (May) 1936.

8. Davis, H. A.: The Physiologic Effects of Administration of High Concentrations of Oxygen in Experimental Secondary Shock, to be published.

tissues. Krogh<sup>9</sup> has shown that the capillaries of isolated muscle, if subjected to deprivation of oxygen, dilate and increase in number, the effect of the changes being to bring about (1) a decrease in the rate of blood flow, which permits greater diffusion of oxygen from the blood to the tissues, and (2) a reduction of the distance between the tissue and the capillaries, which in turn reduces the distance the oxygen must travel from the blood to the tissues. The result of these capillary changes is therefore an increase in utilization of oxygen by the tissues.

That such an increase in utilization of oxygen does occur in cases of dehydration shock has already been shown (Davis<sup>8</sup>). The effects of anoxemia, however, are not limited to the peripheral tissues. The lack of oxygen is felt even more keenly by the central nervous system than by the tissues previously described. Studies of the pathologic changes associated with shock in man suggest that many of these vascular changes are mediated through the central nervous system, which is highly susceptible to anoxemia (Davis<sup>10</sup>).

The exact relation of oxygen deprivation to lesions of the tissues has been studied by other workers. Yant and his associates<sup>11</sup> produced acute anoxemia in dogs by exposing them to atmospheres containing extremely low concentrations of oxygen. The circulatory changes which followed were characterized by perivascular hemorrhages and by dilatation involving the entire capillary system. In addition, histologic evidence of damage to the nerve cells of the brain was found, being most marked in the neurons of the outer granular layer of the cerebral cortex. Similar lesions have been noted in the brains of dogs subjected to prolonged dehydration (Schaferstein and others<sup>12</sup>).

Other workers have studied the effects of chronic exposure to atmospheres containing deficient amounts of oxygen. Campbell<sup>13</sup> exposed animals to low oxygen pressures for seven to thirty-three days and observed the development of a general state of vascular congestion. The lungs showed congestion of the alveolar capillaries, and

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9. Krogh, A.: The Supply of Oxygen to the Tissues and the Regulation of the Capillary Circulation, *J. Physiol.* **52**:457-474, 1919.

10. Davis, H. A.: Pathology of Shock in Man: Visceral Effects of Trauma, Hemorrhage, Burns and Surgical Operations, *Arch. Surg.* **41**:123-146 (July) 1940.

11. Yant, W. P.; Chornyak, J.; Schrenk, H. H.; Patty, F. A., and Sayers, R. R.: Studies in Asphyxia, Bulletin 211, United States Treasury Department, Public Health Service, 1934.

12. Schaferstein, S. J.; Popowa, N. A., and Owtscharenko, E. P.: Experimentelle Exsikkose und Toxikose (Pathologisch-histologische Veränderungen des zentralen Nervensystems, *Jahrb. f. Kinderh.* **145**:210-229, 1935.

13. Campbell, J. A.: Note on Some Pathological Changes in the Tissues During Attempted Acclimatization to Alterations of O<sub>2</sub>-Pressure in the Air, *Brit. J. Exper. Path.* **8**:347-351, 1927.

hemorrhages and free blood pigment were observed in the pulmonary tissues. The capillaries of the liver were extremely congested, particularly in the region of the central veins of the liver lobules. Fatty changes in the cardiac muscle fibers were present, associated with distention of the cardiac vessels and hemorrhages and edema in the myocardium.

Similar fatty changes were observed by Rosin<sup>14</sup> in the hearts of animals suffering from chronic anoxemia. It would seem from these studies, therefore, that anoxemia which is not primarily due to a reduction in blood volume can lead to changes in the tissues resembling those found in cases of shock associated with a reduction of the blood volume.

The significance of the hepatic changes must next be considered. It has already been pointed out that depletion of glycogen in the liver cells was observed, particularly in the midzonal and periportal areas of the liver lobules. Similar changes have been noted in the liver (Davis<sup>15</sup>) after injection of large amounts of epinephrine, and it is possible that the hepatic changes observed in cases of dehydration shock may be the result of an increased secretion of epinephrine. Such a concept receives support from the work of Kellaway,<sup>16</sup> who has demonstrated that anoxemia results in an increased secretion of epinephrine. It is also supported by the work of Freeman and his associates,<sup>17</sup> who have reported an increased secretion of epinephrine in the presence of dehydration. The changes observed in the livers of animals suffering from dehydration shock caused by the withdrawal of water from the tissues in many ways resemble those described by Bardeen<sup>18</sup> and by Belt<sup>19</sup> as occurring in the livers of human beings who have died of burns.

Many similarities to the lesions found in other states associated with hemoconcentration are observed in the changes in the adrenal glands produced by dehydration shock and consisting of distention of the capillary blood vessels, petechial hemorrhages, focal necrosis and leukocytic infiltration. The similar changes which have been noted in the adrenal

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14. Rosin, A.: *Morphologische Organveränderungen beim Leben unter Luftverdünnung*, Beitr. z. path. Anat. u. z. allg. Path. **76**:153-180, 1926.

15. Davis, H. A.: Unpublished data.

16. Kellaway, C. H.: Some Physiological Effects of Anoxaemia, *J. Physiol.* **52**:lxiii-lxiv, 1918-1919.

17. Freeman, N. E.; Morison, R. S., and Sawyer, M. E. M.: Effect of Dehydration on Adrenal Secretion: Relation to Shock, *Am. J. Physiol.* **104**:628-635, 1933.

18. Bardeen, C. R.: A Review of the Pathology of Superficial Burns with a Contribution to Our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns, *Johns Hopkins Hosp. Rep.* **7**:137-179, 1898.

19. Belt, T. H.: Liver Necrosis Following Burns, Simulating the Lesions of Yellow Fever, *J. Path. & Bact.* **48**:493-498, 1939.

glands of human beings dying of burns have been interpreted as evidence supporting the theory of a toxic factor in this condition, but it would seem more reasonable to attribute them to an alteration of the capillary circulation in the glands, resulting from anoxemia.

The exact significance of the infiltrations of polymorphonuclear leukocytes in the adrenal glands is difficult to estimate. Such collections were not observed in other tissues in which similar disturbances of the capillary circulation were evident, and the cause is not clear at this time.

Congestion of the alveolar capillaries, which was present in all the animals, is significant. Disturbance of the pulmonary circulation may produce alterations of the oxygen content of the blood. Harrop and Heath<sup>20</sup> have pointed out that when the blood is concentrated, as in the presence of polycythaemia vera, some alteration in the permeability of the alveolar capillaries also occurs, so that there is a diminution in the diffusion of oxygen from the lungs to the blood. In addition, congestion of the pulmonary capillaries reduces the vital capacity of the lungs (Peabody and others<sup>21</sup>). It is clear that these pulmonary changes may seriously reduce the oxygenation of the blood in its passage through the lungs.

Pulmonary edema, which was present in a number of these animals, must also be considered a factor in decreasing oxygen diffusion from the lungs to the blood. It is probable that it is the result of an increased permeability of the alveolar capillaries, the alteration being the result of several factors. One is the deficient oxygenation of the capillary wall. Another possibility is that the alteration in permeability may be produced through the action of the nervous system. It has been pointed out (Davis<sup>10</sup>) that pulmonary edema is frequently associated with anoxemia of the brain and that it occurs after bilateral vagotomy (Farber<sup>22</sup>).

#### SUMMARY AND CONCLUSIONS

A study of the lesions of the tissues which result from acute experimental loss of water shows them to be correlated with lesions which occur in other conditions associated with hemoconcentration, such as intestinal obstruction and burns. The rapid concentration of blood, whether due to loss of whole plasma (burns, trauma), loss of the protein fraction of the plasma (plasmapheresis) or loss of the aqueous fraction

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20. Harrop, G. A., and Heath, E. H.: Pulmonary Gas Diffusion in Polycythemia Vera, *J. Clin. Investigation* **4**:53-70, 1927.

21. Peabody, F. W.; Blumgart, H. L., and Drinker, C. K.: Effect of Pulmonary Congestion on Ventilation of Lungs, *J. Exper. Med.* **35**:77-95, 1922.

22. Farber, S.: Studies on Pulmonary Edema: Consequences of Bilateral Cervical Vagotomy in Rabbit, *J. Exper. Med.* **66**:397-404, 1937.

of the plasma (dehydration), leads to deficient oxygenation of the body tissues. Certain results follow, such as (1) dilatation and increase in the number of functioning capillaries, which permit an increased diffusion of oxygen from the blood, and (2) increased permeability and dilatation resulting from the local effect of poorly oxygenated blood. It is suggested that the nervous system, which is the most susceptible of all tissues to oxygen deprivation, also plays a part in effecting these capillary changes. The glycogen depletion observed in areas in the liver is the result of a homeostatic increase in secretion of epinephrine.

The alterations described should not be considered pathologic. Rather, they should be considered the anatomic expression of the physiologic changes which the body must make to minimize the effect of oxygen deprivation. Other alterations of the tissues, such as the congestion of the pulmonary capillaries and pulmonary edema, are less beneficial, for they will further diminish the oxygen content of the blood and, as a result, the oxygenation of the tissues.

# NONDESTRUCTIVE TUBERCULOUS POLYARTHRITIS VERSUS TUBERCULOUS RHEUMATISM (PONCET)

## REPORT OF A CASE

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AND

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LOS ANGELES

It is nearly forty years since Poncet<sup>1</sup> described a type of tuberculous polyarthritis which resembles clinically an acute or chronic nonspecific articular disease, especially rheumatic fever or rheumatoid (atrophic) arthritis. The existence of such an entity is still controversial. The following case is among very few in which the tuberculous causation was verified by histologic examination and culture of the articular tissues. Numerous consultations in the United States and abroad reveal the differences and difficulties of interpretation and permit an analysis and evaluation of the conceptions of "tuberculous rheumatism."

## REPORT OF CASE

Mrs. B. R. S., a Jewess aged 34, a teacher, first consulted us in May 1936 for pain in various joints and swelling and contracture of the left knee which had developed during a period of four years.

*Past and Family History.*—In childhood the patient had some of the febrile diseases and also "rheumatic" pains of the arms, feet and back. At the age of 5 years she suffered from eczema for one year. She had contacts with tuberculosis through her mother, who had pulmonary hemorrhages during pregnancy and after delivery of the patient. An uncle who had tuberculosis of the spine and ribs with sinuses was living with the family when the patient was 3 years old. Her father also had a "lung trouble" which years later was finally recognized as tuberculosis. A younger brother had pleurisy, pneumonia and transient pains and swelling of the right knee joint and elbow, diagnosed as nonspecific synovitis. During adolescence the patient frequently had colds and sore throat. A tonsillectomy was performed at the age of 15. At the ages of 19 and 20 she had pleurisy. She lost 40 pounds (18 Kg.) during the following year and was treated for nervous exhaustion and underweight in a sanatorium. Her lungs and heart at this time were found to be normal. At 21 years she had a dry cough for eight months. Her temperature was normal. The following year she had scarlet fever and

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From the Orthopedic Department of the College of Medical Evangelists, White Memorial Hospital.

1. Poncet, A.: Rhumatisme tuberculeux abarticulaire: Localisations viscérales et autres du rhumatisme tuberculeux, Lyon méd. 99:65, 1902.



severe sore throat. At the age of 24 she had attacks of vomiting for several weeks, followed by hoarseness and loss of the voice. At 25 she had a dry cough, and a slight amount of sputum on two occasions was examined and found not to contain the tubercle bacillus. The patient was irritable and extremely tired and spent nineteen days in a sanatorium. Infiltration of both lungs was found, more marked at the right. The larynx was normal. The roentgenograms showed diffuse patchy mottling to about the third rib on both sides, more marked on the right. The greater portion of this mottling was of more recent origin, but there was present some older fibrosis in the right lung. The three day quantity of sputum was 10 cc., and five tubercle bacilli were present per oil immersion field. The urine and the blood count were normal. The patient spent four months in the mountains and gained 20 pounds (9 Kg.). A check-up examination showed no more signs of activity in the lungs. However, at the age of 30, after influenza, she again had sore throat, and a tuberculous ulcer of the larynx was suspected. The teeth were regularly attended. No symptoms of neurologic disease or of disease of the gastrointestinal tract were found.

The menstrual periods started at the age of 11 years, lasted three or four days and were painful at first. At 25 she had pain over the right lower quadrant of the abdomen. She had leukorrhea and occasionally spotting during the interval, for which she received glandular treatment. On several occasions she had amenorrhea, which lasted up to three months. The gynecologic diagnoses up to the present varied. One specialist suspected tuberculosis of the right tube and ovary. Another diagnosed a small fibroid of the uterus. More recently, several gynecologists found the genitalia normal but infantile. The patient had never been pregnant. She practiced contraception.

*Onset and Course of Articular Symptoms.*—Except for the vague rheumatic pains in the arms, hands and feet during childhood and adolescence she did not have any serious articular trouble until the age of 28. In January 1931 she turned in bed abruptly and twisted the left ankle. Pain, swelling and redness developed and persisted for months, in spite of rest in bed for six weeks, physical therapy and strapping. The left knee also became painful and swollen and crepitated on motion. Roentgenograms of the ankle and knee joints revealed no abnormality. In 1934 she was in an automobile collision and suffered sprains and bruises of both ankles. Subsequent pain and swelling developed in the left knee and thigh and were diagnosed as due to thrombophlebitis. She was confined to bed for several weeks, and weight bearing was not permitted for three or four months. Physical therapy was subsequently applied, and contrast baths gave the most relief. For the following years up to 1936 she had recurrent attacks of pain in the hips, gluteal regions, feet, fingers and right arm. However, the pain and swelling in the left knee joint were permanent, and gradually a flexion contracture developed.

*Physical Examination.*—Examinations during 1936 and 1937 revealed the following data: The general condition was good. The patient weighed 126 pounds (57 Kg.). Her height was 60 inches (152 cm.). The temperature was 98 F.; the pulse rate, 82 and the blood pressure, 112 systolic and 65 diastolic. She was surprisingly cheerful considering the long duration of her illness. She walked with a slight limp but was able to teach school, although with effort. No foci of infection were found; the tonsils had been cleanly removed; the throat, nose, eyes and ears were normal. The heart, gastrointestinal tract, abdominal organs and nervous system were normal. The lungs did not show any signs of active tuberculosis. The spine showed slight curvature, with convexity to the left side due to contracture of the left knee and rotation of the pelvis. The left anterior superior

spine was 1 inch (2.5 cm.) lower than the right. Forward and backward bending was normal. She had discomfort in returning to the upright position from forward bending. There was tenderness over the hip joints, but motion was normal. A moderate degree of depression of the longitudinal and metatarsal arches was present. The left knee was tender and was  $\frac{1}{2}$  inch (1.2 cm.) larger in circumference over the patella. No increase of cutaneous temperature nor redness and no varicose veins were found. The infrapatellar fat pad was enlarged, but no fluctuation was present. The angle of greatest extension was 165 degrees; the angle of greatest flexion, 110 degrees. Straight leg raising on the left was 60 degrees, and pain was referred to the knee. There was no grating when the patella was pressed and moved over the femur. A review of old and new roentgenograms showed a narrow joint space in both knees, a small spur on the medial margin of the tibia and beginning roughening of the joint surface over the lateral part of the left tibia. Only a slight decrease of calcium was present, and there was hardly any change in the series of roentgenograms taken during a period of four years (fig. 1). The blood count and the urine were normal. The Wassermann, Eagle and Hinton reactions were negative. Quantitative tuberculin tests with dilutions of 1:100,000 and 1:1,000,000 gave weakly positive reactions. There was also positive cutaneous reactivity to hemolytic streptococci. The rate of sedimentation of the blood was 22 mm. in one hour according to the Westergren method. The condition was diagnosed as rheumatoid (atrophic) arthritis of moderate severity.

*Therapy and Progress.*—The therapy during these two years consisted of extension of the left knee by means of a turnbuckle cast, injections of colloidal sulfur, administration of streptococcus vaccine, histamine iontophoresis and, finally, twelve injections of a colloidal gold preparation. Physical therapy measures were also prescribed for home use. In the diet sufficient caloric intake and raw fruit and vegetables were emphasized, and cod liver oil and concentrated vitamins were also taken. During this period attacks of pain of various duration in the knees and other joints, especially those of the hips, arms and legs, occurred. Occasionally she also had pain in the cervical portion of the spine, radiating into the right arm, with numbness in the fourth and fifth fingers. The attacks were more severe after strains; however, the flare-ups were not followed by permanent disability, and she was able to continue teaching. In July 1937 the patient left for the spa in Pistyany, Hungary. The baths provoked severe reactions. The patient went to Vienna and had a thorough check-up by a number of specialists. Prof. R. Kienboeck, who interpreted the roentgenograms, found in the left knee joint slight atrophy of the bones and thinning of the menisci and articular cartilages; superficial erosion at the intercondyloidal eminences of the tibia; in the left hip joint slight porosis of the head and neck of the femur, and at the lateral sides of the greater trochanter also osteophytes. The ankle joint showed slight porosis, especially of the talus. He made the diagnosis of benign tuberculous rheumatism, Poncet type. The internist, Prof. Carl Reiter, concurred in the diagnosis of Poncet rheumatism. He recommended moderate active and passive motion, heliotherapy and ultraviolet therapy, a sojourn in the mountains during the winter and plenty of fruit and vegetables. The left knee joint was fitted with a brace and received four roentgen treatments. Several gynecologists found a small uterus and hypofunctioning of the ovaries, for which roentgen treatments of the hypophysis and estrogenic substances were given.

After her return she followed the prescribed regimen and resumed teaching in the spring of 1938. She had transitory attacks of pain in various joints and

more continuous pain, periarticular swelling and contracture in the left knee joint. On April 9 she was referred for a check-up to a well known arthritis clinic. Our previous findings and diagnosis of rheumatoid arthritis were confirmed. The patient's general condition was regarded as good. The temperature, blood count and urine were normal, but the sedimentation rate was 60 mm. in an hour. Search for focal infections revealed only slight infection of the postpharyngeal lymphoid



Fig. 1.—Anteroposterior (*A*) and lateral (*B*) views of the left knee joint seven years after onset of symptoms, showing only narrowing of the joint space, small spurs at the inner condyles of the femur and of the tibia and moderate thickening of the synovial membrane of the suprapatellar bursa.

strips, and cultures of material from the throat yielded a pure culture of *Streptococcus viridans*. This organism was also obtained from the cervix of the uterus. There was a moderately high streptococcus agglutination. The left knee joint was aspirated, and only 1.5 cc. of fluid was obtained. This was injected into a guinea pig. The result was later reported to be negative. On the basis of repeated

positive pure cultures of *Str. viridans* it was thought that the disease originated from a diffuse infection of the upper respiratory tract. The weight bearing on the contracted leg and the subluxated tibia were regarded as important factors in perpetuating the disease. Treatment for "streptococcic endocervicitis" and sub-clinical chronic "streptococci pharyngitis" was recommended. The presence of tuberculosis was regarded as exceedingly improbable on the basis of the clinical picture and the absence of progressive roentgen changes during a four year period. After her return she was referred for treatment of the foci of infection. However, the gynecologists did not find streptococci in the cervix and regarded the pelvic organs as bearing no relation to the arthritis. The laryngologist found no pathologic change in the nose and throat but noted a healing tuberculous ulcer of the epiglottis. The patient finished the summer teaching but had increased discomfort and disability in both knees, greater fatigue and transient attacks in other joints. A check-up showed a good general condition, normal temperature and no



Fig. 2.—Gross appearance of the synovial membrane. Note the absence of ulceration. The pinpoint-sized yellowish nodules on the surface are not reproduced distinctly.

activity of the process in the lungs, but the value for hemoglobin was 65 per cent and the sedimentation rate was 40 mm. an hour. Arthrotomy and synovectomy of the left knee were advised in order to restore the most affected joint and to eliminate a source of infection.

A final check-up by an internist did not reveal active visceral tuberculosis. However, an orthopedic consultant regarded the clinical and roentgen picture as indicative of tuberculous arthritis of the left knee joint.

The patient entered the hospital on August 10. The temperature was observed for two days before operation and varied between 98 and 98.6 F.; the pulse rate varied from 60 to 84. On August 12 a synovectomy was performed. The synovial membrane (fig. 2) was red and thickened, especially in the suprapatellar pouch, where adhesions were also present. The surface was velvety and in some places was sprinkled with grayish nodules the size of a pinpoint. In the central cavity a pannus spread along the lateral and medial condyles of the femur into the

intercondylar space and between the crucial ligaments. The pannus attacked more the lateral condyle, which appeared to be squared off. The synovial membrane around the patella was red and hypertrophied. The patella was normal except for a slight marginal erosion. The articular cartilages were normal except in places, where they were covered with pannus. When the pannus was scraped off the surface showed a yellowish color, faceting and superficial erosions. Only a



Fig. 3.—High power magnification of a section of the synovial membrane, showing infiltration of the surface, numerous dilated blood vessels and two miliary tubercles with giant cells.

few cubic centimeters of synovial fluid, mixed with blood, could be obtained. No part of the synovial membrane or of the articular surfaces showed gross destruction or caseation. Frozen sections did not show tubercles. The findings at the operation were more in agreement with a nonspecific, nondestructive inflammatory process until the paraffin sections revealed the tuberculous causation.

*Histologic Picture.*—Paraffin sections taken from the suprapatellar pouch showed a hypertrophic synovial membrane with numerous villi. The surface was intact on large stretches; in other parts it was covered with fibrin, which had started to become organized. The synovial lining consisted of numerous rows of cells in places infiltrated by round cells. The synovial and subsynovial tissue contained miliary tubercles with a central Langhans giant cell surrounded by epithelioid cells, lymphocytes and plasma cells (fig. 3). Rarely, small conglomerated tubercles were present. Caseation or destruction of the synovial membrane was absent. In many places there was only perivascular round cell and plasma cell infiltration of the type associated with nonspecific rheumatoid arthritis.

The section from the lateral part of the synovial membrane, which normally is fibrous, showed the surface covered with fibrin. There was a diffuse infiltration of the synovial membrane and the subsynovial tissue with inflammatory cells. In some places there were obliterated larger vessels in the synovial membrane, but close by newly formed vessels were filled with blood. No tubercles were seen in this part. The synovial membrane from the medial part showed a dense stroma and diffuse infiltration, but in addition fibrotic miliary tubercles were present. Twenty-five sections of different parts and at different levels were stained for acid-fast bacilli, but only two tubercle bacilli were found in a giant cell of one section after thorough search. The Gram-Weigert stain did not reveal any organisms. A guinea pig inoculated with macerated synovial membrane had tuberculosis of the local lymph glands and advanced visceral tuberculosis after six weeks. Dr. Emil Bogen obtained from the organs a pure culture of the human type of tubercle bacilli. Cultures for pyogenic cocci were negative.

On September 3 a Hibbs fusion of the left knee joint was performed. Two Steinmann pins were driven from the tibia into the femur, and a plaster spica was applied.

*Postoperative Course.*—After the first operation the temperature ranged between 98 and 100.8 F. for six days. For the following six days the maximum temperature was 99.4 F. After the fusion operation the maximum temperature was 100.2 F. (on the fourth day). The temperature was normal after fourteen days. One month after the second operation the patient was discharged. Control roentgenograms showed satisfactory callus formation; the wound was draining through a window cut in the plaster cast. On December 6 (three months after fusion) the Steinmann pins were removed. A check-up roentgenogram for fusion was taken and revealed solid bony union between the femur and the tibia. A plaster of paris cylinder cast was then applied. In January 1939 the cast was discarded; a leg brace was fitted, and the patient was permitted to walk on crutches, which were discarded one month later. The brace was discarded two months thereafter. Check-up examinations for the last twenty-six months have shown the fused left knee to be painless. The patient walks with a hardly detectable limp. Her physical condition is satisfactory. She has been teaching school for the last year. However, she complains of attacks of pain in the ankles, hips, fingers and dorsal portion of the spine. She tires easily and is nervous. The attacks of articular pains are generally of short duration. Two months ago she caught a cold and had a dry cough for several weeks. A specialist in diseases of the chest did not find any activity in the lungs, and the sputum did not yield bacilli. Also, the roentgenogram of the dorsal part of the spine showed only porosis and haziness of the intervertebral disks of the eighth and ninth dorsal vertebrae. Quantitative tuberculin tests gave moderately positive reactions with dilutions up to 1:1,000,000 (0.001 mg.).

## COMMENT

Three different preoperative diagnostic opinions were expressed as to the cause of the articular symptoms:

1. The prevalent American opinion, shared by us, diagnosed the condition as a mild rheumatoid (atrophic) arthritis. This opinion was based on the involvement of numerous joints and on the absence of clinical or roentgen evidence of destruction after long duration of the process. Circumstantial evidence was seen in the continued good general condition, normal temperature, absence of activity in the lungs and negative results of guinea pig inoculation with the fluid from the left knee. The history of sore throats and angina following scarlet fever seemed to justify the assumption that the upper part of the respiratory tract was the primary focus, especially as one observer obtained pure cultures of *Str. viridans* from the throat. The correct diagnosis was missed by underestimation of the familial and personal history of tuberculosis and by the refusal to recognize such a mild course of polyarthritis as tuberculous. On the other hand, the evidence of streptococcic focal infection was overemphasized. Certain clinical features which should have aroused suspicion were overlooked, such as: relative lack of involvement of the hands and feet, which are usually among the first joints affected; asymmetric involvement, and attacks rather than continuous progress, which is typical of rheumatoid arthritis. Finally, it was not justifiable to assume that the lack of destruction in the most affected joint was an indication of rheumatoid arthritis. Typical rheumatoid arthritis is also markedly destructive. The guinea pig inoculation was carried out with an insufficient amount (1.5 cc.) of fluid. The negative result therefore does not carry much weight. The elucidation of the factors which were responsible for our misinterpretation is important, because they are typical of the American approach to the differential diagnostic problems of arthritis. The lesson which we have learned is that mild chronic polyarthritis may have a tuberculous causation and that an adequate evaluation of the symptoms is necessary for the discovery of such as an atypical condition.

2. In Vienna, most clinicians and roentgenologists concurred in the diagnosis of tuberculous rheumatism of the Poncet type. Besides the history of previous pulmonary tuberculosis, much emphasis was given to the osseous atrophy of the left knee, hip and ankle joints. Indeed, Professor Kienboeck made the diagnosis solely from the roentgenograms. We do not regard the slight roentgen changes to be in any way characteristic, notwithstanding the final outcome of this case. We concur with the opinion of one Viennese roentgenologist that immobilization and reduced use could have produced the same degree of osseous atrophy. The Viennese observers emphasized the benign character of the disease

because of the prevalent opinion that tuberculous rheumatism is produced by toxins rather than by bacilli, which proved to be erroneous in this case.

3. Finally, the last American consultant favored the diagnosis of tuberculous arthritis of the left knee joint. At the time of his examination the symptoms were confined to this joint. However, a consideration of the whole course and the operative findings show that the condition belonged to a type which is distinct from typical monoarticular destructive tuberculous arthritis. It is true that tuberculous arthritis often affects more than one joint. In a series of 168 cases, Slocumb and Ghormley<sup>2</sup> found involvement of two joints in 13.1 per cent, but in only 5.4 per cent were more than two joints affected. Rarely were more than three joints involved. In 151 cases observed by Kling,<sup>3</sup> multiple articular involvements occurred in 5.9 per cent. However, one or more of these joints showed clinical or roentgen evidence of destruction. It is also admitted that with involvement of recent onset no destruction may yet be detected in a tuberculous joint which later takes a typical course, but absence of destruction of soft and hard tissues during a period of seven years is uncommon. In Kling's<sup>3</sup> series material destruction was demonstrated within a year from onset in 86 per cent of cases, within two years in 96 per cent and within three years in 98.5 per cent. In this case solid bony fusion occurred rapidly after operation, while in cases of typical tuberculous arthritis slow union is the rule.

#### CRITICAL REVIEW OF "TUBERCULOUS RHEUMATISM"

Since Poncet, a large literature has been devoted to the problem of tuberculous rheumatism. Brav and Hench,<sup>4</sup> after a study of two hundred and forty references, came to the conclusion that there is no incontrovertible proof that such an entity exists. Hench and his associates<sup>5</sup> recently confirmed this opinion. Copeman<sup>6</sup> found in a study of nine books and pamphlets and over one hundred articles on the subject only 12 detailed case reports. Of the 12 cases the synovial tissue

2. Slocumb, C. H., and Ghormley, R. K.: Polyarticular Tuberculous Arthritis, *S. Clin. North America* **15**:1251, 1935.

3. Kling, D. H.: Unpublished data.

4. Brav, E. A., and Hench, P. S.: Tuberculous Rheumatism, *J. Bone & Joint Surg.* **16**:839-866, 1934.

5. Hench, P. S., and others: The Present Status of Rheumatism and Arthritis: Review of American and English Literature for 1936, *Ann. Int. Med.* **11**:1108, 1938.

6. Copeman, W. S. C.: On a Tuberculous Factor in the Ætiology of Certain Cases of Rheumatoid (Atrophic) Arthritis, in *Reports on Chronic Rheumatic Diseases*, London, H. K. Lewis Company, Ltd., 1936, no. 2, pp. 24-25.



was examined in 4. Typical tubercles were found once; in 1 case the tissue was questionable but acid-fast bacilli were found; in 2 the tissues showed nonspecific inflammation, with occasional giant cells in 1. Therefore, our case is one of the very few instances in which the diagnosis was proved by the presence of tuberculous synovial tissue, the inoculation of which produced a typical tuberculosis in guinea pigs. In 8 of the cases guinea pigs were given injections of articular fluid; in 5 the results were positive, in 1 questionable and in 2 negative. Inoculation of a guinea pig with synovial fluid in our case also gave negative results. Copeman published 12 cases of rheumatoid polyarthritis which he regarded as having a tuberculous factor. In none of the cases was the diagnosis confirmed by recovery of tubercle bacilli from the synovial fluid or by biopsy of the synovial tissue. The tuberculous factor was definitely established only in the 2 cases in which typical tuberculous arthritis developed later. In 116 cases of rheumatoid arthritis studied by Kling a presumptive diagnosis of tuberculous causation was made in 4, about 2.6 per cent. Of 250 cases of chronic rheumatoid (atrophic infectious) arthritis Brav and Hensch found familial tuberculosis present in 11.6 per cent and active visceral tuberculosis present in 8 per cent. Among 150 cases of rheumatic fever, familial tuberculosis was found in only 10.6 per cent, and tuberculosis elsewhere in the body, in 1.3 per cent. In 45 cases of rheumatoid arthritis under Kling's observation, guinea pig inoculations with articular effusions uniformly gave negative results. Synovectomy on one knee joint was performed in 10 cases of rheumatoid arthritis. The synovial membranes showed only nonspecific inflammatory changes, and stains for acid-fast bacilli gave negative results. In a recent series of 20 cases of rheumatoid arthritis Prof. E. Löwenstein, who is associated at present with the Hooper Foundation at the University of California, was kind enough to carry out his method of cultures for tubercle bacilli in the blood and articular fluids. He obtained only one positive blood culture in this series. The foregoing evidence indicates that tuberculosis is not a frequent factor in rheumatoid arthritis and rheumatic fever.

The failure to establish a definite syndrome and the confusion in the conceptions of tuberculous rheumatism are chiefly due to the following reasons:

1. The description given by Poncet and his followers is of a medley of various types of acute, subacute and chronic polyarthritis with no distinctive clinical features.

2. Too many theories of the pathogenesis were advanced without irrefutable evidence. The most popular is the assumption that in cases of tuberculous rheumatism tubercle bacilli do not invade the joint. Therefore, typical tubercles are absent. The noncharacteristic inflam-

mation is produced by toxins from a tuberculous focus somewhere in the body. However, to date it has not been demonstrated that the tubercle bacilli produce diffusible exotoxins. The different types of tuberculin are endotoxins obtained from emulsions of bacilli or extracts of cultures. Unlike a true toxin, such as diphtheria toxin, tuberculin is not toxic even in large doses when injected for the first time into normal persons.

In the absence of diffusible toxins it is unlikely that articular lesions can be produced through sensitization from a distant focus. With tuberculosis as with any other wasting disease, split products of tubercle bacilli and disintegrating tissue produce nonspecific toxic symptoms, such as loss of weight, fatigue, night sweats and anemia. Noncharacteristic pains in the joints may also occur but do not justify separate classification as tuberculous rheumatism. The assumption of Frugoni and Peserico<sup>7</sup> that certain tuberculins show definite arthrotropism is without foundation. The presence of tubercle bacilli in the joint is a necessary requirement for the development of tuberculous lesions. The mild course of articular diseases in the cases which were regarded as cases of tuberculous rheumatism has been explained by the action of attenuated tubercle bacilli or of an ultravirus. This is not supported by our case, because inoculation produced advanced tuberculosis in the guinea pig within eight weeks, and the cultures yielded the typical tubercle bacilli found in the human being. The evidence is more in favor of a high degree of tissue resistance, which is responsible for the rapid destruction of the invading tubercle bacilli.

#### SUMMARY

On the basis of a detailed case history, a review of our own material and a review of the literature, the evidence is presented that a mild type of tuberculous polyarthrititis does occur. It is due to a hematogenous infection of the joints from a visceral focus in a person who has a high tissue resistance. On the other hand, production of lesions in the joints by diffusible tuberculous toxins is denied. Only the demonstration of tubercle bacilli in the articular fluid or of tubercles in the synovial tissue is an irrefutable proof of the tuberculous causation of any articular lesion. It is not proved that the tubercle bacillus or its products are able to produce other than specific pathologic changes. The assumption of many authors that only conditions in which there are nonspecific lesions should be included under tuberculous rheumatism leads to confusion. The claim of Poncet and his followers that tuberculous rheumatism is a clinical entity without definite pathologic background is not warranted. The lack of a clearcut clinical picture is just what makes

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7. Frugoni, C., and Peserico, M. E.: *Rhumatisme et tuberculose*, *Acta rheumatol.* 4:9, 1932.

the diagnosis uncertain. In the descriptions of Poncet and his followers tuberculous rheumatism mimics all types of acute and chronic arthritis. The tuberculous causation is in the majority of cases either unproved or doubtful. When pathologic evidence has established the tuberculous nature of mild chronic polyarthritis the condition should be designated by its chief characteristic, as nondestructive tuberculous polyarthritis. One can dispense entirely with the confusing term tuberculous rheumatism. In cases of polyarthritis which on clinical grounds is suspected of a tuberculous causation a presumptive diagnosis of nondestructive tuberculous arthritis may be made.

Dr. Emil Bogen and Dr. E. Löwenstein assisted with the cultures in this study.

## News and Comment

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### CONGRESS OF PLASTIC SURGERY

The first Latin-American Congress of Plastic Surgery will be held in Rio de Janeiro and São Paulo, Brazil, July 6 to 12, 1941. The topics to be discussed include "Plastic Trends in Treatment of Wounds." Members of the congress who wish to present articles or to take part in the discussions should communicate with the president of the congress, Prof. A. Prudente, R. Benjamin Constant, 171-1.º Andar, São Paulo, Brazil, thirty days in advance of the meeting. All articles presented will be published in book form. Any person who is interested may become a member of the congress.

## DESTRUCTION OF PROTHROMBIN AND STORAGE OF VITAMIN K

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AND

CORNELIUS VERMEULEN, M.D.

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Patients with obstructive jaundice not infrequently have hypoprothrombinemia within a week after the onset of jaundice. In a previous communication, Livingstone and one of us (Allen) <sup>1</sup> gave evidence that vitamin K is stored in the body and will prevent a precipitous fall after discontinuance of administration of the drug to patients with obstructive jaundice. Lord, Andrus and Moore <sup>2</sup> have likewise concluded from their work that vitamin K is stored and have suggested the liver as the site of storage. Such observations raise the problems of the rapidity of in vivo destruction of prothrombin and the apparent absence of storage of vitamin K.

The intimate association of prothrombin elaboration and the liver is shown in the hepatectomized dog. In such an animal the prothrombin falls to zero within twenty-four hours.<sup>3</sup> Similar disappearance of prothrombin has been produced by chloroform poisoning.<sup>4</sup> This complete loss of prothrombin in such experiments is in sharp contrast to the slow loss of prothrombin activity in plasma maintained at body temperature (four days required to bring the level of prothrombin to

From the Department of Surgery, the University of Chicago.

Aided by a grant from the Douglas Smith Foundation for Medical Research.

1. Allen, J. G., and Livingstone, H.: Studies on the Early Postoperative Reduction of Prothrombin in the Jaundiced and Biliary Fistula Patient with Special Reference to Anesthesia, *Anesthesiology* **1**:89-93 (July) 1940.

2. Lord, J. W., Jr.; Andrus, W. De W., and Moore, R. A.: Metabolism by Vitamin K and Role of the Liver in Production of Prothrombin in Animals, *Arch. Surg.* **41**:585-595 (Sept.) 1940.

3. Warner, E. D.: Prothrombin: Effect of Partial Hepatectomy, *J. Exper. Med.* **68**:831-835 (Dec.) 1938.

4. Smith, H. P.; Warner, E. D., and Brinkhaus, K. M.: Prothrombin Deficiency and the Bleeding Tendency in Liver Injury, *J. Exper. Med.* **66**:801-811 (Dec.) 1937.

50 per cent of normal<sup>5</sup>). It would appear that prothrombin is actively destroyed *in vivo*, at least when the liver is damaged or removed.

A case was observed by us that would indicate active destruction of prothrombin in the presence of an apparently normal liver. A 37 year old woman with a complete external bile fistula, the result of a previous cholecystectomy, had spontaneous hemorrhages fourteen months after the fistula developed. She was given a transfusion of 7,200 cc. of blood over a thirty-six hour period. Bleeding ceased. Within two days, however, spontaneous hemorrhage recurred, despite the fact that the amount of blood given by transfusion approximated the calculated total blood volume of the patient. The prothrombin of the transfused blood apparently was destroyed within this short period. This case emphasizes the futility of transfusion alone in combating hemorrhage due to hypoprothrombinemia.

As there is rapid *in vivo* destruction of prothrombin, one must account for the failure of hypoprothrombinemia to appear until relatively late in some cases, e. g., cases of complete external bile fistula. In the case just mentioned as well as in other cases of external bile fistula we have observed a delay in the appearance of hypoprothrombinemia for one month or more after the complete drainage of bile externally. There must be a constant replenishing of circulating prothrombin in these cases, and there is presumably a reserve of vitamin K which enables the liver to elaborate prothrombin, since further absorption of the vitamin is prevented by the absence of intestinal bile.

Further evidence that vitamin K is stored was obtained in the cases of 3 patients, each with a bile fistula. As soon as each patient disclosed a reduction in prothrombin<sup>6</sup> the following experiment was performed: Eight milligrams of vitamin K (menadione; 2-methyl-1, 4-naphthoquinone) was administered with bile salts over a twenty-four hour period. With this dose the prothrombin rose to a normal level by the following day. As soon as a normal level of prothrombin was obtained, administration of the drug was discontinued and the time necessary for prothrombin deficiency to appear again was recorded. In none of these patients did the prothrombin remain at the normal concentration longer than twenty-four hours after cessation of vitamin therapy. If, however, the drug was again administered, this time for from four to five days, four to six days elapsed after its discontinuance before the onset of prothrombin reduction appeared (see table). To 1 of these patients a third course of vitamin K (see chart) was administered; this time the drug was given for eleven days. In this instance normal prothrombin

5. Allen, J. G.: Unpublished data.

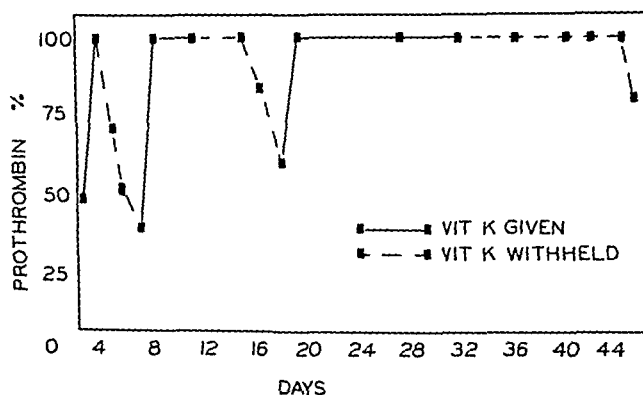
6. Allen, J. G.; Julian, O. C., and Dragstedt, L. R.: Use of Serial Dilutions in Determination of Prothrombin by the One Stage Technic, *Arch. Surg.* **41**:873-878 (Oct.) 1940.

activity was maintained for twelve days after administration of the drug was stopped.

The data on these 3 patients constitute conclusive evidence that vitamin K in some form is stored within the body and permits the elaboration of prothrombin by the liver as long as the stores hold out.

*Correlation of Duration of Vitamin K Therapy and Period of Maintenance of Normal Prothrombin Level after Discontinuance of Drug*

Complete External Bile Fistula	Number of Days of Vitamin K Therapy	Number of Days Prothrombin Level at 100 per Cent After Drug Discontinued
Case 1 (2 courses of vitamin K).....	1 4	1 5
Case 2 (2 courses of vitamin K).....	1 5	1 5
Case 3 (3 courses of vitamin K).....	1 5 12	1 6 13



A patient with a bile fistula and prothrombin deficiency received three courses of vitamin K—bile salt therapy. It is apparent that the longer the therapeutic period the greater the time before the onset of hypoprothrombinemia after administration of the drug is discontinued.

In this manner the continued destruction of prothrombin in vivo is compensated, so that a constant level of plasma prothrombin is maintained.

The concept of vitamin K storage and the recognition of the rapid in vivo destruction of prothrombin have immediate application in surgical practice. It becomes evident that treatment of hypoprothrombinemia with just sufficient vitamin K to raise the prothrombin content of the blood to normal will not insure against hemorrhage except for very short periods. It is necessary to continue treatment beyond this point to build up a reserve within the body before operation or to continue

treatment postoperatively until vitamin K in adequate amounts can be taken in the food. Unless this is done the prothrombin content of the blood will fall rapidly after cessation of treatment, with danger of consequent hemorrhage.

Unfortunately, at present there is no method of measuring the vitamin K reserve. Apparently a patient may be at the point of depleting his reserve and still have a normal level of plasma prothrombin. Accordingly, it would seem wise to administer vitamin K when there is obvious defective absorption even though the prothrombin content of the blood is not decreased, since the reserve may soon be exhausted.

It appears that damage to the liver greatly hastens the appearance of hypoprothrombinemia. This is illustrated in cases of obstructive jaundice as compared with cases of biliary fistula. That this fall in prothrombin is not due to the inability of the impaired liver to make prothrombin is evidenced by the usually rapid response in cases of obstructive jaundice to treatment with vitamin K. If it is assumed that the site of vitamin K storage is the liver, it seems likely that damage to the liver may result in a partial or total destruction of this substance or that the vitamin is stored in a form which the damaged liver cannot utilize for the elaboration of prothrombin. This may be the explanation for the unusually rapid fall of plasma prothrombin in persons exhibiting damage to the liver coupled with deficient absorption of vitamin K. Experimental work is in progress to determine whether this assumption is correct.

#### SUMMARY

Further evidence is presented indicating a rapid *in vivo* destruction of prothrombin in man.

Failure of prothrombin to fall immediately after the development of a complete external bile fistula is explained on the basis of the storage of vitamin K.

It is emphasized that the prothrombin determination does not indicate the state of the body reserves of vitamin K.

It is essential that preoperative vitamin K-bile salt therapy be carried out in cases of jaundice or of bile fistula even though the initial preoperative level of prothrombin is normal, as the body stores may be virtually depleted of the vitamin.



## HYDATID CYST OF THE LIVER

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I have mentioned in a previous publication some of the pathologic changes which may appear in a person with hydatid cyst of the liver, especially one affecting the adventitia. I shall now describe some of the clinical forms of hepatic hydatosis, with particular attention to the treatment.

In 85 per cent of cases hydatid cyst of the liver is situated in the right lobe; in only 15 per cent is it located in the left. In either location it may have an anterior or a posterior evolution, but a cyst of the left lobe usually directs itself forward (fig. 1) and ends by protruding onto the epigastrium, where it can be reached by a midline laparotomy (see paragraph 1 in section on technic).

The most common type of cyst of the liver, i. e., that of the right lobe, may be central or peripheral. If it is central it does not alter the shape of the liver to a large extent, though the volume of this organ slowly increases as if hypertrophy of the parenchyma had set in. If it has a peripheral localization it has either a thoracic or an abdominal evolution and accordingly protrudes backward or forward.

A cyst with an anterior thoracic evolution pushes forward the costal margin and makes it appear more or less widened at that level. Such a cyst may be reached either through a high laparotomy (see paragraph 2 in section on technic) or by means of a transdiaphragmatic parapleural thoracolaparotomy (see paragraph 3 in section on technic).

A cyst of posterior thoracic evolution (fig. 2) pushes the diaphragm and the inferior lobe of the right lung upward, thus deepening the corresponding costodiaphragmatic recess, the walls of which come closer together as the cyst grows larger. The surgeon cannot reach it without opening the pleura and cutting through the diaphragm (see paragraph 4 in section on technic).

A cyst of anterior abdominal evolution (fig. 3 A) usually appears from under the costal margin. When it comes from the quadrate lobe it protrudes under the rectus abdominis muscle, but if its original site

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This is the second article on hydatid disease contributed by Dr. Arce at the suggestion of the Chief Editor of the ARCHIVES.



Fig. 1.—*A*, hydatid cyst of the left lobe of the liver (pneumoperitoneum). The shadows of the heart, the diaphragm and the right lobe are clearly seen in a normal condition. The left lobe is totally occupied by the tumor. *B*, same patient before pneumoperitoneum was present.

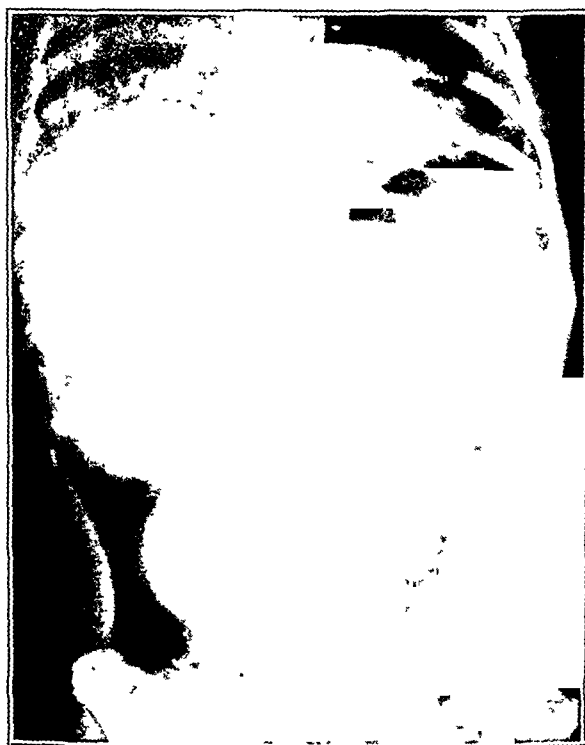


Fig. 2.—Hydatid cyst of the right lobe of the liver (pneumoperitoneum). The shadow of the right hemidiaphragm is greatly raised. The heart and the diaphragm are distinctly seen in normal condition. The right lobe is totally occupied by the tumor, and the left lobe is increased in size (vicarious hypertrophy).

is in the vertical portion of the right lobe it appears to the right of the vesicular line. In most cases its clinical appearance is that of a smooth, round tumor following the liver in its movements. It generally emerges from the liver in the shape of a sphere or a segment of a sphere. Sometimes it is so peripheral that it leaves the liver *en masse*, in such a fashion that its attachment to the gland depends on whether it is sessile or pedunculated. This is a true emerging type of tumor, and the increase of volume on the part of the liver is localized. This last feature allows differentiation from a central cyst, as the latter screens its abdominal evolution behind a diffuse hypertrophy of the liver (fig. 3 *B*.) A hydatid cyst of the liver always causes vicarious or compensating hypertrophy of the parts of the organ which are not affected by its

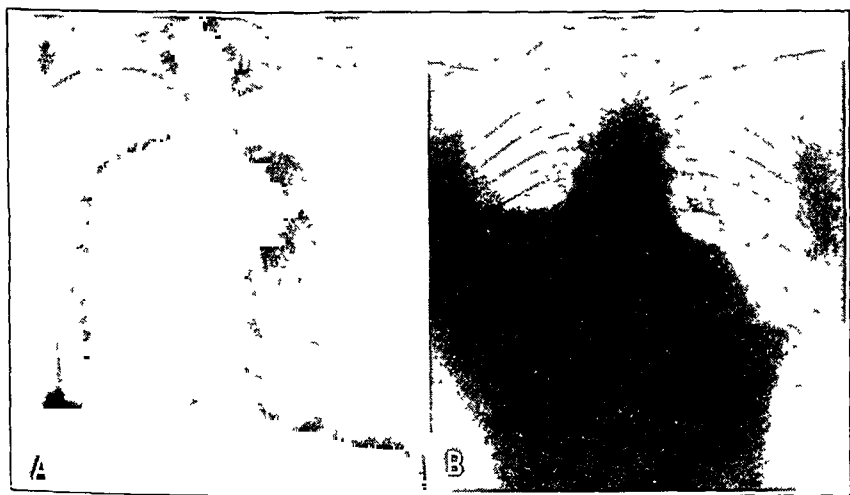


Fig. 3.—*A*, huge hydatid cyst of the right lobe of the liver (abdominal evolution). The shadow of the liver is seen above that of the cyst; above this appears the air from the pneumoperitoneum, and still higher is the diaphragmatic dome. *B*, huge central cyst of the liver. There is diffuse hypertrophy of the whole organ.

presence. This is better noticed in the left lobe; as hydatid cysts of this section of the gland is less common, an increase in size should be carefully checked to avoid mistaking the bulge for a cyst (fig. 2).

As a rule, a cyst of anterior abdominal evolution comes into contact with the posterior aspect of the anterior abdominal wall; there the surgeon finds it by means of a laparotomy performed immediately above the tumor. I always resort to a transverse laparotomy, with or without dissociation of the muscle fibers (see paragraph 5 in section on technic).

A cyst of posterior abdominal evolution comes into contact with the posterior abdominal wall. If it comes from the vertical portion of the right lobe it is related to the right kidney; this has more than once led

the surgeon to mistake such a cyst for a renal tumor. A cyst originating in the caudate lobe protrudes farther in and pushes forward the components of the hepatic hilus (bile duct, portal vein and hepatic artery). A cyst of the former type is accessible either through a lumbotomy as performed for renal trouble or by means of a low transverse laparotomy at the level of the twelfth rib (see paragraph 6 in section on technic). A cyst of the caudate lobe is dealt with through a transverse laparotomy, the same as that used for a cyst of abdominal evolution.

#### TECHNIC

*Laparotomies.*—A cyst of the liver must be reached by the shortest route between the skin and the tumor. The following variation should therefore be adapted to the peculiarities of each case.

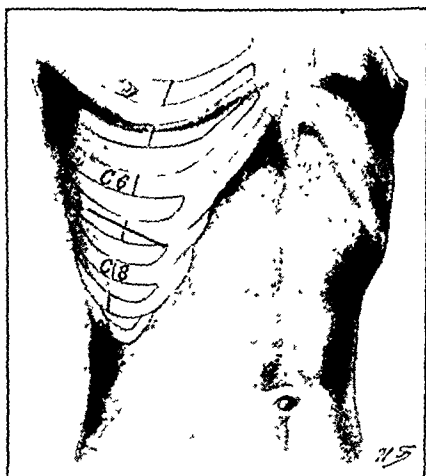


Fig. 4.—Cutaneous incision for a transdiaphragmatic parapleural laparotomy.

1. *Midline Laparotomy:* This incision needs no description. There is no objection to carrying out the incision either to the right or to the left of the midline, so as to interpose two aponeurotic layers between the cyst and the skin. When the cyst bulges behind the left rectus abdominis muscle I use the transverse instead of the vertical transmuscular laparotomy.

2. *High Laparotomy:* A transverse incision is made which goes from one edge to the sheath of the right rectus abdominis muscle, on the tumor's salient. The anterior wall of the sheath, the muscle and the posterior wall are then cut transversely; the cyst appears as soon as the last-mentioned structure is cut, as the peritoneum is closely attached to the posterior wall of the sheath. This type of incision offers the following advantages: It is relatively small; its direction allows the surgeon to see clearly through it, and it is usually large enough for the ulterior treatment of the cyst. If necessary, it can be easily and safely enlarged

by extending it to the right as far as the costal margin or to the left even farther away than the midline.

3. Transdiaphragmatic Parapleural Laparotomy: This operation is carried out in four stages.

In the first stage a cutaneous incision is made over the ninth, eighth or seventh costal arch, reaching in front the costal cartilages and on the other end as far as 4 or 5 cm., behind the costochondral joint on the

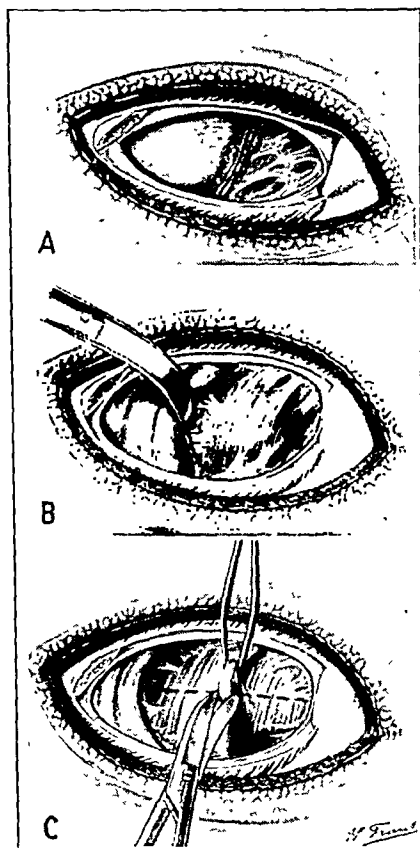


Fig. 5.—Technic of transdiaphragmatic parapleural laparotomy. See text for explanation.

naked rib (fig. 4). According to the costochondral arch selected, this incision will have a more or less pronounced upper concavity.

In the second stage the aponeurosis and the muscular section of the rectus abdominis muscle are cut, the anterior end of the rib being thus exposed.

The third step is to remove the entire costal cartilage, including the part of the costochondral margin corresponding to this arch, and 3 or 4 cm. of the rib. This must be performed with the utmost care to avoid damaging the underlying structures. It is especially at the level

of the posterior surface of the rib that the greatest care should be taken not to interfere with the pleura. On the bottom of the operative wound the surgeon can recognize the diaphragm inside the costo-diaphragmatic recess and outside. The recess can be easily detected because it ascends obliquely upward and forward; it is marked by some yellowish fatty tissue, and there is sometimes a small vessel which follows the same direction obliquely upward and forward (fig. 5 *A*).

In the fourth stage, with a blunt dissector the pleural recess, together with its surrounding structures, is pushed upward and backward (fig.

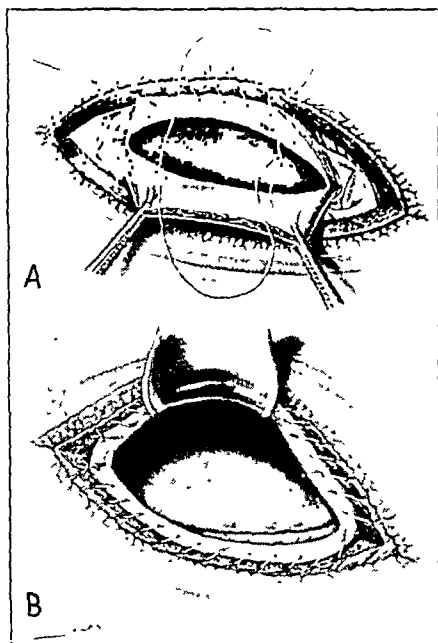


Fig. 6.—Technic of transpleural transdiaphragmatic thoracolaparotomy. See text for explanation.

5 *B*) so as to avoid opening the pleura and to expose a more ample zone of the diaphragm. As soon as the diaphragm is cut (fig. 5 *C*), the convex surface of the liver and the cyst can be seen. As is easily understood, this incision requires exact preoperative localization of the tumor, but I prefer it to mobilization of the costal margin, a technic called after Lannelongue by French surgeons.

4. Transpleural Transdiaphragmatic Thoracolaparotomy: This operation, usually called Israel's, is directed toward the posterior part of the ninth rib, between the midaxillary and the scapular line. After resection of about 8 to 10 cm. (3 to 4 inches) of rib, the pleura and the diaphragm are opened throughout the wound; care should be taken to avoid causing a pneumothorax. The pneumothorax can be avoided by the following procedure: The upper and the lower edge of the diaphragmatic incision

are held with a three-toothed or four-toothed forceps and are "herniated" (fig. 6 *A*) until they are brought into contact with the muscles under the cutaneous incision. Both resulting edges are then sutured, first with disconnected stitches and later with a running suture, which will insure perfect adaptation of both edges (fig. 6 *B*). In this way the pleural cavity becomes isolated from the wound, and any contamination or irritation of the pleura is thus avoided. This procedure of muscular suture, taught by one of the greatest Argentine surgeons of the beginning of the century, Posadas, is in all lights preferable to that recommended by most authors, i. e., the suturing of both pleural layers before opening them. After Posadas' procedure has been carried out, the posterior part of the convex surface of the liver, in which the cyst is contained, appears in the bottom of the wound. Frequently the liver or the tumor

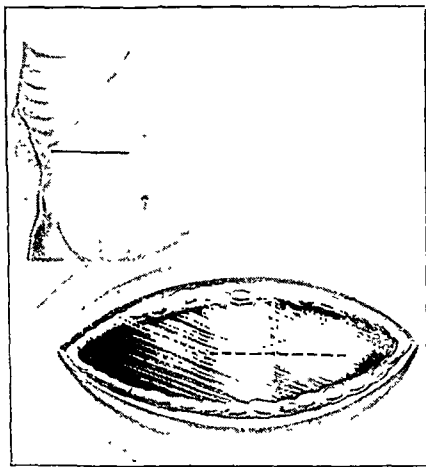


Fig. 7.—Arce's laparotomy incision.

has become adherent to the under surface of the diaphragm in such a fashion that edges of the diaphragmatic incision cannot be "herniated." If this is the case, the surgeon should not hesitate to carry the wall muscles to the diaphragm so as to make the aforementioned suture for the protection of the pleural cavity.

5. Arce's Laparotomy: Since I made it known in 1918, I use my own incision, called in Argentina Arce's gridiron transverse laparotomy, for all surgical conditions of the biliary system and for those of the right lobe of the liver (hydatid cysts included). This incision is the application in the upper part of the abdomen of McBurney's gridiron incision for appendicitis. It is carried out in four stages:

(a) Starting on the costal margin at the level of the anterior end of the tenth rib, a horizontal incision of the skin and subcutaneous tissue is made, which ends at the midline (fig. 7). Often, particularly in women, it is carried out along a neighboring crease.

(b) Another horizontal incision is made which on its inner half opens the anterior wall of the sheath of the rectus abdominis muscle, while the outer may have an upward direction in order to dissociate the muscular fibers of the external oblique muscle (fig. 7).

(c) An incision is made downward and outward for the separation of the fibers of the internal oblique muscle. These fibers start on the lateral border of the sheath of the rectus abdominis muscle and descend in an outward direction (fig. 8 A).

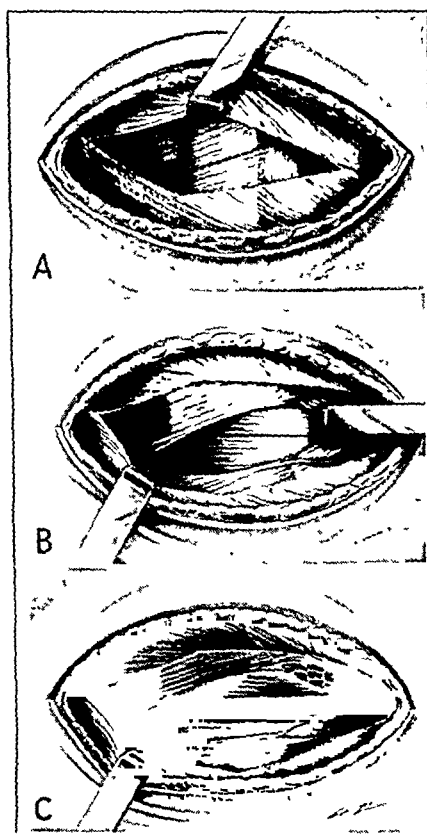


Fig. 8.—Technic of Arce's laparotomy. See text for explanation.

(d) A horizontal incision is made which will dissociate the fibers of the transverse abdominis muscle and at the same time open the peritoneum (fig. 8 B). The rectus muscle is either set aside (fig. 8 B) or cut transversely (fig. 8 C). Its section is no obstacle to the formation of a good postoperative scar, nor does it favor the ulterior formation of a hernia.

Once the abdomen has been opened, the right upper quadrant of the abdominal cavity (infrahepatic fossa) is exposed. The surgeon can then reach easily nearly any cyst with an abdominal evolution, par-



ticularly if it comes from the right lobe (which it most often does) and can treat it accordingly.

6. Transverse Laparotomy of the Flank, or Low Transverse Laparotomy: A horizontal incision is made, starting on the right twelfth rib and ending inside and in front on the mamillary line. This is followed by incision of the fibers of the external oblique muscle and of the internal oblique muscle, which run in the opposite direction to those of the external oblique muscle.

Dissociation of the fibers of the transversus abdominis muscle and opening of the peritoneum are then carried out.

This laparotomy facilitates the exploration of: (a) the kidney; (b) the posteroinferior portion of the right lobe of the liver; (c) the space between the ascending colon and the lateral wall of the abdomen, and finally (d) the ascending colon itself. Through this incision a posteroinferior cyst of the liver with a lumbar evolution is within easy reach. If necessary the incision may be extended backward, either by resecting the twelfth rib or by going a bit lower without touching it, thus enabling the surgeon to approach the renal fossa. It is therefore most useful in cases in which there is difficulty in differentiating between tumor or cyst of the liver and a similar growth arising from the kidney.

It is always advisable to make the operative wound in the tumor's salient on the skin, and in order to make this point more evident I resort to the "liver position" used in midline laparotomies as well as in transverse and gridiron incisions. This position is obtained by "breaking" the operative table at the level of the liver so as to provoke an exaggerated artificial lordosis. The operative table is first placed in an oblique position, opposite to that of Trendelenburg (head up, feet down), and then only the upper section of the table (the one where the head and thorax are lying) is lowered; thus the upper part of the abdominal, epigastric and hypochondriac regions are directly exposed.

*Treatment of the Cyst.*—Once the surgeon is in contact with the cyst, it can be treated in any of four different ways: (a) removal of the parasite followed by suture of the adventitia without drainage; (b) removal of the parasite followed by marsupialization and drainage of the adventitia; (c) removal of the parasite without suturing or draining the adventitia, and (d) total removal of the cyst.

For the first three alternatives several procedures must be previously carried out.

1. Protection of the Operative Field: The abdominal cavity or the raw surface of the operative wound may become infected by daughter vesicles or scolices if they come into contact with cystic contents in which the parasite is alive. This actually takes place when the adventitia is incised, and the infection occurs through graft of the cystic contents. If the echinococcus is dead and the cyst has turned septic, the peritoneum

and the operative wound become infected by the germs present in the septic contents. It follows that in either case it is of the utmost importance to carry out a detailed protection of these two structures, so as to avoid their coming into contact with the parasite when the cyst is emptied.

Gauze towels surrounding the tumor constitute the best means of protection. One end is left outside the wound; so the same towels that isolate the cyst from the peritoneal neighborhood protect the raw surface of the wound as they emerge from the abdomen.

2. Puncture of the Cyst and Evacuation of the Parasite: Through the adventitia the cavity of the cyst is reached by means of a large trocar, which may or may not be attached to a suction apparatus. I use both the large trocar and the suction device. If the latter is in good working order and the trocar is of the right size (0.01 to 0.025 mm., according to the size of the cyst), the entire contents—fluid, membrane and daughter vesicles, if any—pass through the trocar into a large flask of 10 liter capacity. A vacuum of  $\frac{1}{2}$  to  $\frac{2}{3}$  atmosphere has been created in this flask, which can be controlled by an ordinary metallic manometer attached to it. Sometimes, either because the suction device is not working properly or because the trocar becomes stopped, it is necessary to withdraw the latter and remove the obstruction and then, either with the same trocar or a new one with no mandrel but with a blunt end shaped like a spoon, evacuate the rest of the cyst's contents. The suction power should not be increased lest bile appear through the small bile ducts opening on the inner aspect of the adventitia or merely separated from the cystic cavity by a very thin wall.

3. Cleansing of the Cystic Cavity: Once the evacuation stage has come to an end, the trocar is set aside and the puncture is enlarged with a scalpel. This step will allow the speculum maneuver (Arce) and the appropriate cleansing of the inner surface of the adventitia. The latter is carried out through a vaginal speculum introduced into the cystic cavity. The valves of this instrument are opened, and by moving it sideways the entire cavity and the adventitial wall can be easily visualized.

The remaining fluid, membranes, daughter vesicles, etc., are removed with gauze towels held by large clamps which, according to circumstances, have straight or curved branches. This cleansing of the adventitial wall should be carried out with the utmost care, so as to leave the cavity absolutely clean, but at the same time very gently, so as to avoid any damage. It should be remembered that the membrane is in some sections composed only of the thin walls of small bile ducts. Often the gauze towels are withdrawn tinted with bile.

4. Previous Formaldehyde Treatment: In spite of the carefully protected operative field and the suction, it is impossible to prevent

some fertile elements of the parasite coming into contact with some structures or remaining attached to the adventitia. It must be remembered that these elements (proliferous vesicles, scolices, etc.), if conditions are favorable, can become grafted on any tissue and reproduce a hydatid cyst.

In order to avoid this, Dévé suggested replacing the hydatid fluid with a 2 per cent concentration of the standard (40 per cent) solution of formaldehyde in water; provided it is left for at least five minutes in contact with the fertile parasitic elements, this solution will "fix" and kill them. After five minutes the formaldehyde solution and the cystic contents are withdrawn prior to the proper cleansing of the cavity.

This procedure with solution of formaldehyde is performed as follows: The cystic fluid is removed through a puncture made on the cyst with a trocar attached to a rubber tube. Through a funnel on the other end of the rubber tube the solution of formaldehyde is introduced in an amount equal to that of the fluid removed. A double stream trocar permitting the washing of the cavity with this solution can also be used to advantage.

5. Treatment of the Adventitia: When the parasite has been removed, one proceeds to deal with the adventitial pouch.

If the cyst is not septic, I use Posadas' procedure, i. e., suture without drainage of both the adventitia and the cutaneous incision. Some surgeons, using the same stitches which close the adventitia, attach the latter to the incision of the abdominal wall. The reason for this is to facilitate the reopening of the pouch if perchance any complication appears in it (for instance, infection, leakage of bile or hemorrhage).

The presence of small bile ducts open in the adventitial pouch is no obstacle to closure of the pouch without drainage. But if a fair amount of bile is present it is advisable to resort instead to marsupialization.

If the cyst is septic it must be evacuated and drained. This is achieved through marsupialization of the pouch, i. e., suturing the edges of the incision of the adventitia to the peritoneum and the deep aponeurotic layer of the abdominal incision. Neither the abdominal superficial layers nor the skin should be used for marsupialization, as this would probably cause postoperative hernia as well as large and ugly scars.

Marsupialization should also be carried out in the case of a cyst open in the biliary tract or in the bronchi.

Lastly, marsupialization and drainage are indicated:

1. For a cyst in the process of regression, with which one frequently finds either calcification of the adventitia or gelatinous degeneration of the parasitic membranes.

2. For a cyst containing little or no fluid but full of membranes.

3. For a cyst full of daughter vesicles, which in some cases are so numerous that they fill the entire adventitial pouch.

4. In any case in which the surgeon is not sure of having evacuated the whole of the adventitial contents.

Once the hepatic wound has been sutured to that of the abdominal wall, one or more tubes of a size in accordance with the depth of the adventitial pouch are introduced therein.

The surgeon should exercise great care in cleansing the pouch and the wound, even if he is leaving a drain. Drainage is carried out only with the purpose of waiting for the organic reactions which will give rise to cicatrization of the adventitial pouch and the abdominal wound by second intention. *The object of drainage is not to leave a way open for the exit of the parasite; the echinococcus should be evacuated during the operation.* It is therefore important to use suction, the speculum and any other device which will insure total evacuation of the adventitial pouch during the operation.

If the edges of the adventitial incision cannot be brought into contact with those of the incision in the abdominal wall, as sometimes happens, it is necessary to resort to indirect marsupialization. This is done without sutures and by means of one or more rubber tubes which reach the bottom of the adventitial pouch. Between the hepatic incision and the operative wound these tubes are protected by gauze in order to favor the formation of adhesions, the isolation of the tube and the creation of an extraperitoneal tunnel between the pouch and the skin.

The postoperative course of a marsupialized cyst should be followed closely. External dressings should be changed as often as is deemed necessary for the avoidance of irritation of the skin, which is frequent in cases in which bile is discharged, and of secondary infection. The rubber tubes may be changed but should not be removed altogether until there is certainty that the adventitial pouch has disappeared and only a communicating tunnel remains.

In cases of calcification or partial necrosis of the adventitia the fistula persists for months and even years, until the calcified or necrotic zones have been totally eliminated.

In cases of multiple abdominal cysts with pouches which once evacuated could be closed without drainage but which are situated at a certain distance from the abdominal wall and therefore offer difficulties to the operation as previously described, it is advisable to follow Mabit's technic. Mabit, a French surgeon, who lived for many years in Argentina, advocated leaving one or more pouches without closure or drainage. He stated that the cicatrization of these cysts left open inside the abdomen will be met by a reactional defense of the body, but he insisted that it should be carried out only when there is no other alternative and when the cysts are small and not infected.

6. Total Removal of the Cyst: There are cases in which a hydatid cyst has become pedunculated and remain attached to the liver only by a thin fibrous or parenchymatous stalk. Such a cyst can be totally

removed, the adventitia included, as if it were a benign tumor. The same applies to a type of emerging cyst which, though sessile, is scarcely included in the liver, its position favoring total removal at the expense of removal of a small portion of the liver. This type of cyst is exceptional.

#### CYST WITH CALCIFIED ADVENTITIA

A cyst with total or partial calcification of the adventitia is observed from time to time; preoperative roentgen examination will allow the surgeon to establish the diagnosis. If the calcification is partial or small

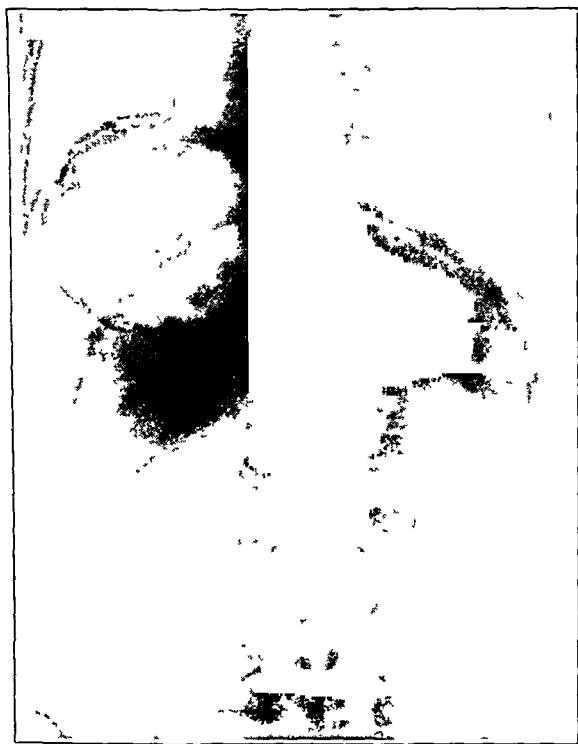


Fig. 9.—Calcified cyst before operation.

the cyst should be treated as if the process did not exist, but if it is total or almost total—as I have observed in some cases (fig. 9)—the treatment differs.

A marsupialized calcified adventitia means postoperative treatment for months and even years, i. e., until the calcified zones are totally eliminated and the wound has completely healed. The resulting long-standing fistula represents the possibility of the patient becoming weak, susceptible to other diseases (tuberculosis) and liable to undergo degenerative processes (amyloid degeneration), all of which may endanger his life.

Thus the surgeon, if the process of calcification is total or almost total, has three paths to follow: (1) not to operate if the cyst is not causing the patient major inconvenience; (2) to marsupialize the adventitia and expose the patient to the aforementioned risks, and (3) to enucleate the entire tumor. I shall refer only to the last-mentioned procedure.

A calcified cyst is usually less adherent to the surrounding hepatic tissue than is an ordinary cyst. In view of this fact and of the fact that the calcified adventitia offers enough resistance to the surgeon's finger, a blunt instrument or a curved periosteotome, the cyst can be isolated from the liver. If the hydatid tumor is situated in the periphery of the liver, the blood vessels and bile ducts that the surgeon meets when about to remove the cyst are few and small; so the cyst can be isolated and removed in a few minutes. In short, the total enucleation of a hydatid cyst of the liver with totally or almost totally calcified adventitia can be tried out when the cyst is not large and is not situated at too great a distance from the periphery of the gland.

Once the cyst has been removed, the surgeon is faced with a diffuse and sometimes abundant hemorrhage in the place formerly occupied by the tumor. This will be stopped by means of gauze swabs previously soaked in hot saline solution, and if this is not sufficient the cavity should be packed with a large gauze towel with the ends protruding through the cutaneous incision. This packing can be slowly removed, starting on the sixth day after the operation, or it can be left in situ, only the external dressing being changed. After the tenth or the twelfth day it can be easily extracted, owing to the fact that the blood serum has soaked it and made it loose. If there is no further hemorrhage a loose packing may take its place, but if blood continues to appear through the wound—a very rare occurrence—the cavity should once more be tightly plugged.

This enucleation of a small peripheral cyst with calcified adventitia bears no relation whatever to the partial hepatectomy and total removal of any hydatid cyst advocated by some Russian surgeons. This procedure, in my opinion and according to my experience, is unthinkable.

#### HYDATID CYST OPEN IN THE BILIARY SYSTEM

In its eccentric growth a cyst of the liver may sometimes come into contact with the secondary biliary duct to such an extent that the parasitic membrane, through a process of slow corrosion of the duct wall, can replace the latter in a small zone. As a result of a trauma or a biliary infection, a rupture of this membrane may occur. This causes the contents of the cyst to pass into the biliary system and give rise to a hepatic colic or to obstruction of the bile duct by daughter vessels, fragments of membranes, etc.

Whether infected or not, such a cyst must be marsupialized after careful cleansing of the adventitial pouch. Once the cause of these complications has been removed, there are two different possibilities to bear in mind, i. e., whether the disturbances disappear or persist. In the first instance disinfection of the biliary tree and duodenal intubation may be tried in order to insure a definite cure of the complication. Surgical intervention is positively uncalled for, and the surgeon's endeavors should be directed only to the healing of the adventitial pouch. But if the obstruction of the bile duct shows no signs of disappearing in spite of medical treatment and duodenal intubation, a choledochotomy with drainage may prove advantageous. The object of this operation is to free the bile duct from the obstructing parasitic elements and to drain the biliary system by means of a rubber tube left in the duct.

Still another set of circumstances may be observed. An obstruction of the bile duct by a hydatid cyst may be diagnosed through the presence of daughter vesicles or fragments of membranes in the stools (hydatid-enteric), but the surgeon may be unable to localize the position of the cyst, which in these circumstances is usually central. Under such circumstances the surgeon should not hesitate to open, free and drain the bile duct. Through this incision he will be able to explore the liver and localize the cyst. If he finds it and surgical circumstances permit, the tumor must be opened, evacuated and drained, but if conditions are unfavorable the removal of the cyst should be left for a second operation.

If the cyst cannot be localized and the patient has fully recovered from the operation, the choledochotomy will allow the injection of iodized poppyseed oil into the biliary tree. The substance will reach the cavity of the cyst, and a roentgenogram taken immediately afterward may show some signs which would permit its localization.

#### HYDATID CYST OPEN IN THE BRONCHUS

The adventitia of a septic hydatid cyst of the liver with a thoracic evolution may become adherent to the diaphragm and through this muscle to the inferior lobe of the right lung. A true pleuroperitoneal symphysis is thus created, which will not allow the cyst to open into either of these serous membranes. This process is the origin of hepatization of the lung and the subsequent suppuration of the inferior lobe, into whose large and medium-sized bronchi the contents of the cyst find their way. Once this process has opened into the lumen of a bronchus, a characteristic vomica of membranes, bile, etc., takes place. The spontaneous opening shows no signs of healing, and the condition of the patient rapidly deteriorates. The sole remedy for this complication is to operate; once the cyst has been localized, the adventitial pouch should be marsupialized after careful evacuation of its contents. The patient soon improves after this surgical intervention, and total healing follows eventually.

# PROGRESSIVE POSTOPERATIVE GANGRENE OF THE SKIN

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Progressive postoperative gangrene of the skin is a rare disease which has been recognized as a clinical entity within comparatively recent times. Surgeons are indebted to Meleney for defining its characteristics and bacteriologic aspects. In Great Britain, Stewart-Wallace summed up the subject in 1935. Since publication of his paper, in which he recorded 37 cases collected in the period from 1908 to 1935, the condition has been reported about 40 times. It is still uncommon, for few surgeons have observed cases personally, and it is doubtful whether it is widely known, although it is now described in some textbooks (Dodd; Rose and Carless).

This paper reports the cases of 2 patients under the care of one of us (J. W. H.). Strangely enough, these patients were treated coincidentally and were the first ones with this condition seen in an active surgical experience of thirty years. A new feature in the case of 1 of them is that the gangrene occurred after a suprapubic prostatectomy. This is the only such instance so far reported.

## REPORT OF CASES

CASE 1.—Mrs. F. B. was admitted to the hospital on April 26, 1939, for acute abdominal pain. Operation (J. W. H.) was performed on the same day, with a mid-line incision. A gangrenous appendix was removed, and pus in the pelvic cavity was drained. The patient's condition improved, but the wound continued to discharge pus freely. On May 17 a gridiron incision was made over the cavity. Pus was evacuated. Tube drainage was used, the central tube being left in. A fecal fistula developed. During the next three months the edge of the wound, which was dirty and unhealthy looking, was treated with eusol<sup>1</sup> packs. From this time

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Because of the difficulties of transatlantic transportation, at the suggestion of the Editorial Board papers from European countries are being published without waiting for return of the authors' proofs.

\* The degrees of the authors were not listed after their names when the manuscript was received. In the sources available in the headquarters office Dr. Geiser's degrees could not be found.

1. Eusol is a solution prepared by adding 12.5 Gm. of chlorinated lime and 12.5 Gm. of boric acid to 1 liter of water.





A



B

*A*, postoperative gangrene of the skin after suprapubic prostatectomy and after guttering of the skin with the diathermy beyond the margin of the wound. *B*, gangrenous abdomen after acute perforative appendicitis with drainage. Note the prolapsed cecum.



onward, the edge of the wound gradually became gangrenous, the gangrene extending outward in all directions. From time to time the gangrenous edges were excised, which caused much pain and tenderness. The patient experienced little discomfort as long as the dressings were not disturbed.

The pus on culture yielded a mixed growth of *Bacillus coli* and staphylococci. There were no actinomycetes. Organisms observed later were gram-negative coliform bacilli and gram-positive cocci. On culture a mixed growth of *Bacillus proteus*, staphylococci and *Streptococcus longus* was obtained. Autogenous vaccines were given but had no effect. The red blood cell count was 2,860,000 and the white blood cell count 12,000 per cubic millimeter. The value for hemoglobin ranged between 46 and 56 per cent.

The gangrene gradually spread until it occupied an area practically covering the right half of the abdomen and, to a lesser degree, the abdominal muscles. The fecal fistula persisted, and about 4 inches (10 cm.) of the bowel projected outside the surface.

The wound was dressed at varying intervals with hydrogen peroxide, eusol,<sup>1</sup> acriflavine, mercury biniodide, dettol<sup>2</sup> and red lotion.<sup>3</sup> None of these had any effect.

Finally, with the cautery an incision was made  $\frac{3}{4}$  inch (1.9 cm.) outside the gangrenous edges through the whole skin of part of the area, and the gutters thus made were swabbed with pure phenol. A dressing of 5 per cent zinc peroxide paste was applied.

Up to within three weeks of death the general condition of the patient was surprisingly good; then she became exhausted and died. (Two blood transfusions were performed; the first caused improvement, and the second produced anaphylaxis after about 4 ounces [120 cc.] of blood had been given.)

CASE 2.—Mr. C. H. B. was admitted to the hospital on July 10, 1939 for acute retention of urine due to an enlarged prostate. Suprapubic cystostomy was performed. On July 24 the value for blood urea was 26.5 mg. per hundred cubic centimeters. The urea concentration test yielded values as follows: before administration of urea, 0.5 per cent; after administration, 0.8 per cent.

The patient's condition was good, and prostatectomy was performed. Operation was a little difficult, as a number of small fibrous areas were encountered. An intravenous injection of 5 per cent dextrose in physiologic solution of sodium chloride was given. On July 28 his condition was much improved. On August 2 the upper portion of the cutaneous wound looked unhealthy; the edges were slightly discolored. Signs of postoperative gangrene developed on August 8. The edges of the wound were tender and painful. Various antiseptic dressings were used.

On August 18 a swab from the wound yielded pus, which on culture produced *B. coli* and *Str. longus*. On August 20 the tissue showed large numbers of coliform bacilli and short chain streptococci. Culture yielded a heavy growth of *B. coli* and a small growth of *Str. longus*.

On August 21 the urine had a specific gravity of 1.025 and was alkaline, with a trace of albumin. Culture yielded a heavy growth of *B. coli* and *B. proteus*.

On August 27 the bladder was septic and edema of the penis developed. The bladder was washed out daily, but a urethral abscess developed. Incision of the whole skin around the wound was performed with diathermy, and the gutter

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2. Dettol is a proprietary antiseptic derived from a coal tar product.

3. Red lotion is a solution of zinc sulfate in diluted compound tincture of lavender.

was swabbed with pure phenol and packed with 5 per cent zinc peroxide paste on cotton gauze tucked under the edges and over the gutter. Rapid improvement took place, so that the gangrenous edges completely disappeared and healthy granulations of the cutaneous edges followed. Unfortunately left hemiplegia developed, probably from an embolus; the patient became weaker; basal pneumonia supervened, and he died on September 13.

*Comment.*—The operator (J. W. H.) had not previously observed a case of this kind in thirty years' experience. In comparing cases 1 and 2 it is obvious that with Mrs. B. (case 1) much valuable time was lost in failing to carry out the treatment by incision, which in the case of Mr. B. (case 2) proved successful.

Consultation with a colleague (H. D.) led the operator to adopt the cautery method of incision. The organisms found in the 2 cases appeared to be identical.

It would seem that the moment such a condition occurs drastic surgical treatment must be undertaken to prevent spread, in much the same way as amputation is done for other forms of gangrene in limbs. That antiseptic dressings have no effect and that only zinc peroxide is of any use must obviously mislead those surgeons who, like the present operator, have been accustomed to adopt the usual methods of treatment of such conditions.

Exactly what causes this type of gangrene seems impossible to say. Every possible channel of infection by all the known methods was explored: the theater, the instruments, the catgut and the theater staff. The throats of the operator, two house surgeons and the nurses were examined bacteriologically, and a streptococcus was found in four nurses and two house surgeons.

Case 3 is presented by permission of Mr. Henry R. Thompson, F.R.C.S., who was responsible for the successful treatment of the patient.

CASE 3.—F. H., aged 67, was admitted to the hospital with a diagnosis of acute intestinal obstruction from a carcinoma of the rectum, 15 cm. from the anus.

On Dec. 16, 1939, laparotomy and left inguinal colostomy were performed. A catheter was inserted into the colostomy stoma, but this was pulled out on the way back to the ward. One hour later the wounds were soaked with liquid feces.

On December 23 there was a large subcutaneous abscess in the upper part of the paramedian wound. On December 31 there was edema of the ankles and legs. By Jan. 7, 1940, this had subsided. On January 13 perineoabdominal excision of the rectum was done. The anterior wall of the rectum was opened but immediately sutured. The growth was perforated. Fat was sutured over it. A left paramedian incision was made for the abdominal portion. The colostomy wound was excised and the lower part of the bowel removed. Both wounds were drained. The skin of the paramedian wound was closed with tension buttons and that of the colostomy wound with silkworm gut sutures.

On January 19 the patient was incontinent of urine. On January 20 an abscess with foul pus from the paramedian wound was drained. On January 27 urine was obtained from the perineal wound, and a fistula into the bladder was

demonstrated by injection of indigo carmine. On February 10 (thirty days after the operation) a slough of the paramedian wound was first noticed. It was very painful. By February 13 the slough had spread circularly and was greenish gray with raised mauve edges, passing to a surrounding area of bright red skin. On February 14 it was treated by diathermy and excision of the gangrenous tissue,  $\frac{3}{4}$  inch (1.9 cm.) from the affected part. On February 18 the bladder was drained by catheter. On February 20 a pathologic report read as follows: "Direct films revealed degenerate pus cells, necrotic debris, staphylococci, streptococci and gram-negative bacilli. No spore-forming organisms and diphtheroid bacilli were seen. Aerobic cultures revealed staphylococci, short chain streptococci and occasional gram-negative bacilli. Anaerobic cultures revealed streptococci of two varieties, fine and coarse, and various gram-negative bacillary forms."

On February 23 a Thiersch skin graft was applied to the affected raw area, which was granulating steadily. On February 27 the skin graft was satisfactory. Urine was still obtainable from the perineal wound.

On March 3 a report on the gangrenous specimen of skin read as follows: "The appearance is that of a fragment of gangrenous tissue in which with Gram's stain short chain streptococci can be seen. Peripherally, numerous areas showing purulent infiltration are present. In parts of the specimen fragmentation and degeneration of muscle fibers are evident."

On March 21 the perineal wound was still wet; otherwise the patient was well. On March 28 a portion of the rectus muscle, removed at an operation one hour previously, was applied to the vesical fistula. On March 30 the muscle graft was removed; it was firmly adherent.

On April 5 the perineal wound was dry. On April 17 the patient was discharged home, well.

#### REVIEW OF LITERATURE

We have collected the cases of postoperative gangrene of the skin from the British, American and Scandinavian literature, and some from the French and German literature, since 1935.

We have also examined the 37 cases cited by Stewart-Wallace. The number of cases collected is 87. From these we have attempted to extract the principal points.

*Classification.*—The cases can be broadly divided into two classes. The first and largest (table 1) includes those in which gangrene occurred after operations on abdominal and thoracic viscera; the other group (table 2) contains those in which the disease followed minor parietal lesions.

The latter contains cases of conditions which do not fully conform to the title of the disease and may not be true examples of it, as they were not all progressive, were not confined to the skin and were not all postoperative.

In the cases represented in table 3, the predominance of the gangrenous appendix and of empyema was outstanding.

In contrast to the previous group, which followed lesions of the viscera, mainly the abdominal viscera, the conditions due to parietal lesions were superficial (table 4).

TABLE 1.—*Gangrene Following Visceral Lesions*

Author	Patient's Sex	Patient's Age	Cause	Bacteria	Treatment	Time of Onset, Days	Result	Duration of illness, Months
1921 Christopher.....	M	64	Empyema; thoracotomy	Gram-positive cocci in chains; gram-negative bacilli	Antiseptic dressings; excision; cauterization	7	R	4½
Gullen.....	M	50	Abdominal abscess (appendical); drainage	Streptococci	Cautery	7	R	4
Borelli.....	F	46	Inflammatory disease of pelvis	Staphylococci; hemolytic streptococci	.....	14	R	21
1926 Alexander.....	M	53	Appendical abscess; appendectomy; drainage	Staphylococci; hemolytic streptococci	Antiseptic dressings; excision; sunlight; foreign protein	5	R	5
Maveda.....	M	38	Appendical abscess; drainage	B. coli; streptococci; staphylococci; diphtheroid bacilli	Excision; thermocautery	..	R	..
Clinton.....	M	38	Appendectomy; drainage	Streptococci; staphylococci; diphtheroid bacilli; B. coli; gram-positive bacilli	10% solution of sodium chloride; cauterization	7	R	3
Brewer and Melency.	M	32	Appendectomy; drainage	Nonhemolytic microaerophilic streptococci; hemolytic staphylococci	Incision; dressings with 1% concentration of 40% solution of formaldehyde	5	R	2
Brewer and Melency.	M	64	Appendectomy; drainage	.....	Excision	..	R	..
Porter.....	F	35	Cholecystectomy	.....	Cautery	..	R	2
Whipple *.....	F	63	Cold abscess in abdomen; incision; drainage	.....	.....	..	R	..
Moscowitz.....	M	48	Appendectomy; drainage	.....	.....	..	R	..
Gordon.....	M	38	Abdominal abscess (appendical); drainage	Gram-positive cocci; Str. pyogenes; diphtheroid bacilli	Antiseptics; ultraviolet irradiation	5	D	12
1928 Mitchell.....	M	70	Appendectomy	.....	.....	..	R	80
Gillespie.....	M	39	Appendectomy	Gram-positive cocci; streptococci; gram-positive diplococci	Excision and cauterization	..	R	7½
Shpley.....	M	..	Abscess of abdominal wall (apical?)	Gram-positive cocci; nonhemolytic streptococci	Cautery; antiseptics	18	R	4
Cole and Heldenman..	M	34	Appendectomy; drainage	Hemolytic staphylococci; umbus	Antiseptics; emetine; excision with cautery	8	R	..
1930 Tennant.....	F	61	Ventral hernia; herniotomy	.....	General antiseptic	..	R	..



TABLE 1.—*Gangrene Following Visceral Lesions—Continued*

Author	Patient's Sex	Patient's Age	Cause	Bacteria	Treatment	Time of Onset, Days	Result	Duration of Illness, Months
Brown, Brown and Murphy †	M	50	Appendectomy; drainage	Staphylococci; gram-negative bacilli; gram-positive diplococci	Excision with cautery	5	R	2
Duelling and Elston †	M	42	Perforated gastric ulcer	Streptococci; staphylococci; gram-negative bacilli	Excision with cautery	13	R	3½
Tunman †.....	F	58	Cholecystectomy	Hemolytic streptococci; B. proteus	Excision	..	R	5
1935 Stewart-Wallace....	M	44	Empyema; thoracotomy	Streptococci; staphylococci; diphtheroid bacilli	General antiseptic	28	D	8
Holmuer and Jaeger §	F	11	Appendectomy (simple)	Nonhemolytic streptococci; gram-negative bacilli	Excision with electric knife	Few days	R	36
Kaplis.....	M	56	Appendectomy; (appendical) abscess	Hemophilic bacilli; B. proteus	Antiseptic dressings	10	D	5
Stohr and Nierland	M	65	Herniotomy	Theoretically nonbacterial	Antiseptic dressings	7	D	1½
Kneppers.....	F	44	Cholecystectomy	Staph. albus; B. coli	Intravenous dextrose; vaccine; arphenamine	21	R	8
Blaxland (case 1)...	M	62	Empyema	Streptococci; staphylococci	Excision; burning out	7	D	9
Blaxland (case 2)...	F	49	Incision of subphrenic abscess	Streptococci	Antiseptic dressings; vaccine	3	R	3
Holman (case 2)....	F	42	Appendectomy (simple)	Staph. aureus; hemolytic streptococci; partially streptococci	Excision with diathermic knife	..	D	45
Hicken.....	F	58	Empyema	Nonhemolytic streptococci; Staph. aureus; diphtheroid bacilli	General; maggots; cautery	43	R	2½
1936 Sehlink and Thomson	F	29	Puerperal cellulitis of parametrium; incision; drainage	Hemolytic streptococci; Str. viridans; Staph. aureus	Excision	..	R	40
Niehingale and Bowden	M	57	Perforated duodenal ulcer	Streptococci; staphylococci	Excision with diathermic knife	10	R	4
Cox.....	M	44	Perforated duodenal ulcer	Str. pyogenes	Antiseptics; excision	7	R	3
Liedberg (case 1)....	M	52	Appendectomy (gangrene)	Variety of cocci and bacilli	Excision	4	D	5
Willard.....	F	57	Appendectomy (gangrene)	Hemolytic staphylococci; non-hemolytic anaerobic streptococci	Excision with scalpel; thermocautery	19	R	..
Syme and Bryce....	M	67	Appendectomy (gangrene)	Aerobic streptococci; diphtheroid bacilli; B. coli; staphylococci	Excision	3	R	3





TABLE 2.—*Gangrene Following Parietal Lesions*

Author	Patient's Sex	Patient's Age	Cause	Bacteria	Treatment	Time of Onset, Days	Result	Duration of Illness, Months
1909 Luckett *	M	55	Furuncle in abdominal wall; incision	Staph. aureus; anaerobic bacilli	Thermocautery	..	R	1
1928 Probststein and Seelig	F	35	Mammary abscess	Staph. aureus	Excision	7-14	R	12
Kreeke *	M	52	Carbuncle in abdominal wall	Hemolytic streptococci; Staph. albus	General	21	D	5
1930 Gudnovskaja *	M	36	Furuncle in abdominal wall	Streptococci; staphylococci	General	..	R	1½
Ballin and Morse...	M	4	Abscess in inguinal region; incision	.....	Cautery	..	R	24
1932 Kupplis (case 1)....	M	72	Incision of furuncle on leg	.....	Conservative; amputation later	..	D	8
Kupplis (case 2)....	M	50	Sympathectomy on thigh	.....	Antiseptic dressings	21	R	30
1934 Diebold.....	F	29	Incision of abscess on shin bone	B. proteus vulgaris; micrococci	Excision	..	D	9
1935 Holman (case 1)....	F	25	Incision of axillary abscess	Hemolytic streptococci; Staph. aureus	General; maggots	..	R	16
Holman (case 3)....	F	20	Axillary abscess	Aerobic: Str. viridans; hemolytic streptococci Anaerobic: Staph. aureus; Str. viridans; hemolytic streptococci	General; excision; maggots	..	R	20
Holman (case 4)....	M	48	Picking of pus-tule on thigh	B. pyocyaneus; hemolytic streptococci; Staph. aureus; no anaerobes	Cautery	2	R	2
1936 Liedberg (case 2)....	F	32	Purulent mastitis; incision	Different types of staphylococci, aerobic and anaerobic	Excision with diathermic knife	4	R	4½
1937 Wachs (case 1)....	F	24	Umbilical abscess (post partum)	Staphylococci; streptococci; gram-negative bacilli; B. coli	.....	..	D	1½
Wachs (case 2)....	F	74	Abscess in groin after irreducible hernia	Staphylococci; streptococci; gram-negative bacilli; B. coli	.....	..	D	1½
Wachs (case 4)....	M	26	Small infections on hands	Staphylococci; streptococci; gram-negative bacilli; B. coli	Burning out; amputation	..	R	5
Wachs (case 5)....	F	66	Varicose ulcer	Staphylococci; streptococci; gram-negative bacilli; B. coli	Cautery; amputation	..	R	2

\* Cited by Knapik.

It will be noticed (tables 3 and 4) that all the conditions, whether due to parietal or to visceral lesions, with two exceptions (those due respectively to herniotomy and to sympathectomy) were primarily due to infection.

The visceral lesions exceed the parietal in the ratio of 4 to 1.

**Prevalence of Male Patients:** Table 5 reveals the striking predominance of male over female patients, the proportion being 12 to 5. Further analysis shows that the parietal lesions were distributed equally between the two sexes (8 to 8). Visceral conditions occurred more frequently in male patients (3 to 1 [53 to 17]). The cause of this is speculative. We hazard the suggestion that it is due to the skin of the male trunk being thicker, coarser and more hairy than that of the female. Thus, staphylococci are inevitably in the hair follicles, and the introduction of virulent streptococci into the skin with a needle gives the condition which Meleney mentioned as requisite for the development of the gangrene, that is, simultaneous inoculation with staphylococci and streptococci.

**Age Incidence.**—In determining the age groups 35 was taken as the datum line. In patients below the age of 35 the incidence of visceral and that of parietal lesions were about equal, being 9 and 8 respectively. In those above the age of 35 the ratio of visceral to parietal lesions rose steeply, to 8:1 (61:8).

**Sex Incidence.**—**Patients Under the Age of 35:** Of a total of 9 patients with visceral lesions 6 were males and 3 were females, and of the 8 patients with parietal lesions 2 were males and 6 were females.

**Patients Over the Age of 35:** There were 61 patients with visceral lesions, 46 men and 14 women, and 8 patients with parietal lesions, 6 men and 2 women.

**Etiology.**—The majority of the patients (69 of 86) were over 35. This indicates that progressive postoperative gangrene of the skin is associated with declining vitality. General debility may therefore be a significant etiologic factor.

Stohr and Niederland expressed doubt whether organisms are the sole cause of the condition. Brandberg also questioned whether a symbiosis of staphylococci and streptococci as described by Meleney is sufficient to cause gangrene of the skin, and he suggested that the cause is a deficient power of reaction on the part of the patient to the long-standing infection. Lynn also noted the low state of general health as significant.

**Time of Onset.**—The time of onset of the gangrene after the operation was reported in 61 cases and was generally within three weeks.

Of 62 cases the onset in 25 occurred in the first week, in 18 in the second and in 11 in the third.

*Bacteriologic Picture.*—The standard of bacteriologic detail is variable; therefore, no attempt has been made to produce figures relative to Meleney's theory that the condition is due to a symbiosis of a microaerophilic streptococcus and a nonspecific staphylococcus.

TABLE 3.—*Data on Visceral Lesions*

	Total Number of Patients	Male	Female
1. Appendectomy			
(a) For gangrenous appendicitis, perforating appendicitis or abscess of appendix.....	34	30	3
(b) For simple (acute) appendicitis.....	4	2	2
2. Emphyema .....	9	7	2
3. Cholecystectomy .....	5	..	5
4. Subphrenic abscess .....	4	3	1
5. Perforated gastric ulcer .....	3	3	..
6. Perforated duodenal ulcer .....	2	2	..
7. Herniotomy .....	2	1	1
8. Acute intestinal obstruction .....	2	2	..
9. Cecostomy .....	1	1	..
10. Suprapubic prostatectomy .....	1	1	..
11. Inflammatory process in pelvis.....	2	..	2
12. Cold abdominal abscess .....	1	..	1
13. Swelling of scrotum .....	1	1	..
Total.....	71	53	17

TABLE 4.—*Data on Parietal Lesions*

	Total Patients	Male	Female
1. Axillary abscess.....	2	..	2
2. Mastitis.....	2	..	2
3. Boil in abdominal wall.....	3	3	..
4. Abscess in groin.....	2	1	1
5. Abscess on shin bone.....	1	..	1
6. Umbilical abscess.....	1	..	1
7. Varicose ulcer.....	1	..	1
8. Sympathectomy on thigh.....	1	1	..
9. Furuncle on lower limb.....	1	1	..
10. Infection on hand.....	1	1	..
11. Pustule on thigh.....	1	1	..
Total.....	16	8	8

TABLE 5.—*Sex of Patients*

	Total	Visceral	Parietal
Male.....	61	53	8
Female.....	25	17	8
Not reported.....	1	..	..
	87	70	16

In 9 cases of visceral and 2 cases of parietal lesions the bacteriologic data were not given.

There appear to be two types of infection: (a) mixed and (b) single.

All of the parietal lesions except a mammary abscess were caused by mixed infection. In this abscess *Staphylococcus aureus* was found.

**Parietal Mixed Infection:** The table of cases reveals the varied combinations of organisms found. The predominant germ was some form of streptococcus—a hemolytic streptococcus, *Streptococcus viridans*, an anaerobic streptococcus or an aerobic streptococcus.

Staphylococci, mainly *Staph. aureus*, were equally frequent, which tends to confirm Meleney's conclusion.

**Visceral Mixed Infection:** Some form of streptococcus was a consistent feature in almost every case in which the lesions were visceral. Staphylococci were as frequent. Superimposed on these were the intestinal organisms, such as *B. coli*, *B. proteus* (5 times), amebas (once), diphtheroid bacilli (6 times) and pneumococci (once). Diphtheroid bacilli and pneumococci were not confined to empyema but were present in some acutely diseased appendixes and in a perforated gastric ulcer. *Bacillus pyocyaneus* appeared twice.

**Diagnosis.**—The characteristic features of progressive postoperative gangrene of the skin as described in the literature and observed by us are:

1. Steady progressive destruction of the skin and subcutaneous tissue, but not of the muscles, fascia or deeper structures. It usually begins in the stitch holes and progresses until the entire trunk is denuded of skin unless death or suitable treatment intervenes.

2. Great pain in the gangrenous edges of the wound, with fair constitutional condition, although there is moderate variable pyrexia.

3. The simultaneous occurrence of streptococcic and staphylococcic infection.

4. The fact that all treatment, including administration of vaccines and serums, with the exception of the cautery, is useless.

It is interesting that two writers (Philipowicz; Kappis) referred to the condition as hospital gangrene. In the experience of both the condition followed visceral lesions. Kappis experienced difficulty in differentiating between progressive and hospital gangrene. He used as his pathognomonic sign the fact that the former is not infective.

**Treatment.**—Stewart-Wallace reported that excision of the area by the cautery or by guttering through surrounding healthy skin is the most dependable treatment. Progressive healing by granulation follows.

This remedy has been generally applied in the cases reported since it has been applied either by thermocautery or by electrocautery, especially in the successful cases. Of 22 fatal cases, the cautery was used in 8, while of 65 cases in which recovery occurred the wound was cauterized in 52.

One case of spontaneous recovery has been reported (Wakeley and Willway).

Two other methods of treatment have emerged. These are (a) the use of maggots and (b) excision by scalpel.

**Maggots:** The introduction of maggots into the wound was reported by Coakley and Klein and by Holman in 1935. The former authors succeeded in clearing up with maggots a condition which had persisted in spite of electrosurgical excision.

The maggots were introduced in counted numbers. They seemed to exercise themselves on the necrotic tissue.

Holman tried this therapy in 3 cases. In 1 the maggots would not stay in the wound, and the patient died. (Rats leaving the sinking ship?) The patients in the other 2 cases recovered.

**Excision by Scalpel:** Willard in 1936 published a case of gangrene following appendectomy in which the entire lower abdominal wall was involved and in which treatment was successful. He excised the area, the sloughs and the spreading edge in the skin with the scalpel, afterward dressing it daily with a watery suspension of zinc peroxide.

**Results.**—The results were reported in 85 cases and are numerically summarized in table 6.

TABLE 6.—*Results of Treatment*

	Recovery	Death	Not Reported	
Total patients.....	63 = 72.4%	22 = 25.3%	2	87
Visceral lesions.....	52 = 73.2%	17 = 23.9%	2	71
Parietal lesions.....	11 = 68.7%	5 = 31.3%	..	16

**Time of Recovery.**—Study of the duration of the illness emphasizes its chronicity. There were 2 quick recoveries (in one month); 5 patients were well in six weeks. Thirty-two patients took two to six months to improve.

Recovery is still possible after the gangrene has existed six months, for 17 patients, 12 with visceral and 5 with parietal lesions, overcame infections of more than half a year's duration. Four of the patients with gangrene following parietal lesions were well in three months.

**Time of Death After Onset.**—Analysis of the reports on the time of death after onset shows that more than half of the deaths (13 of 22) occurred from three to nine months after the onset; 6 took place in three months, and 2, after more than nine months.

**Age at Deaths.**—There were 22 deaths in all. Three occurred among the 17 patients under 35 years of age. The remaining 19 occurred among the 69 patients 35 years of age and over.

The death rate for visceral lesions was 24.3 per cent, as compared with 31.2 per cent for parietal conditions.

Of the patients who died from visceral lesions, 16 of 17 were over 35 years of age, the mortality being 26.2 per cent. This is in contrast to the mortality observed in patients under 35, which was 11.1 per cent.

Of the 16 patients in whom the disease followed parietal lesions, 8 were under 35 years of age. This is in contrast to the data on patients with visceral lesions, among whom the proportion was 9 of 61. Among patients below 35, 2 died, and in the older group (8 patients), 3 died, totaling 5 of 16.

#### SUMMARY AND CONCLUSIONS

Three new cases of progressive postoperative gangrene of the skin are reported.

The cases published since 1935 are abstracted. A table of all cases found in the literature is given.

Certain clinical features of the disease are brought forward, including the general debility of the patients.

Emphasis is laid on the need for early diagnosis.

It is concluded that the best treatment is prompt excision of the edges of the wound with the cautery.

Another successful remedy is the introduction of maggots into the wound as described by Holman.

Skin grafting accelerates healing.

Gerald Merton, M.A., Ph.D., supplied the color photographs.

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# METASTASIS OF PRIMARY CARCINOMA OF THE BREAST

WITH SPECIAL REFERENCE TO SPLEEN, ADRENAL GLANDS  
AND OVARIES

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The literature on the sites of metastasis of primary carcinomas of the breast consists of amazingly few specific contributions. Of course, all leading textbooks and comprehensive studies of tumors in general and of cancers of the breast in particular refer to the various locations of the metastatic deposits, but they either mention only the lymph nodes, lungs, liver and bones or refer to old, apparently out of date studies on this subject. Thus, Ewing<sup>1</sup> in 1940, in regard to sites of metastasis, cited Gross's<sup>2</sup> work on carcinoma of the breast, a study published in 1888, when as a rule only macroscopic evidence of metastasis was available. There are reports of a few instances of what were thought to be unusual sites of metastasis, or one may find rarely a series of cases of carcinoma of the breast with metastases. Most often, however, either the latter are clinical reports without postmortem observations or it is not clear whether a postmortem examination was performed and, if so, whether the various organs were examined histologically. As a matter of fact, there is only one recent study available which specifically states that postmortem material was available and which lists the various organs involved by carcinoma primary in the breast. This is the study of Warren and Witham.<sup>3</sup>

It was thus deemed advisable first to study the material available in the department of pathology of the Michael Reese Hospital with special

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From the Departments of Pathology and Surgery of the Michael Reese Hospital.

1. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

2. Gross, S. W.: *A Clinical Study of Carcinoma of the Breast and Its Treatment*, *Am. J. M. Sc.* **95**:219, 1888.

3. Warren, S., and Witham, E. M.: *Studies on Tumor Metastasis: The Distribution of Metastasis in Cancer of the Breast*, *Surg., Gynec. & Obst.* **57**:81, 1933.

concern for the sites of metastasis of carcinoma of the breast. Though we realized that the material, comprising only 43 autopsies on patients with primary carcinoma of the breast, was rather scant, a study of this was considered worth while because it included a histologic examination of the various organs to determine whether they showed tumor involvement grossly and because the histories of the patients were available. Secondly, it was considered important to investigate, on the basis of a careful histologic examination, the aptitude for metastasizing of any one type of primary carcinoma of the breast. Also, because of the nature of the material at hand, the interval between operation (radical mastectomy) and death could easily be established, and it was thought that perhaps some information could be gathered thus concerning the prognosis as judged from the type and the histologic appearance of the tumor. Since in a few instances the clinical diagnosis was not made and the autopsy revealed the primary tumor and many metastases, the publication of these cases was considered important.

After this material was compiled, it was found that the adrenal glands, ovaries and spleen were involved in a rather surprisingly large number of instances. Because of this it was considered interesting to compare our data with those in the various reports in the literature in regard to metastases in these three organs. In the following sections a short outline of the pertinent literature is given in respect to the location of metastases, with especial reference to metastases in the spleen, adrenal glands and ovaries.

#### LITERATURE

As has been stated, Ewing<sup>1</sup> cited Gross's work, done in 1888, on metastatic growths. Gross<sup>2</sup> reported 114 cases of carcinoma primary in the breast. The pleura was involved in 17; the lungs in 41; the ovaries in 3; the spleen in 5; the kidney in 5; the adrenal glands in 1; the liver in 42, and the bones in 18. In 423 collected autopsies the percentage of metastases from primary carcinoma of the breast in various organs was as follows: ovary, 8; spleen, 4.7; kidney, 5.7; adrenal glands, 1.8; liver, 48.6, and bones, 20.5.

Török and Wittelshöfer<sup>4</sup> in 1880 reported 336 cases of cancer of the breast. The spleen was involved in 13, the ovaries in 26 and the adrenal glands in 6. Paget,<sup>5</sup> in 1889, studied 735 necropsies of patients with cancer of the breast. He found metastasis in the liver in 241 cases, in the spleen in 17, in the kidneys or adrenal glands in 30 and in the

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4. von Török, G., and Wittelshöfer, R.: *Zur Statistik des Mammacarcinoms*, Arch. f. klin. Chir. **25**:873, 1880.

5. Paget, S.: *The Distribution of Secondary Growths in Cancer of the Breast*, Lancet **1**:571, 1889.

lungs in 70. Williams<sup>6</sup> in 1894 found the ovaries and spleen each involved once, and the adrenals twice, among 44 carcinomas primary in the breast. Campiche and Lazarus-Barlow<sup>7</sup> in 1904 studied 470 cases. The spleen was involved 13 times, the adrenal glands 35 times and the ovaries 24 times. Handley<sup>8</sup> in 1922 studied 53 instances. Among metastases in various organs, the liver was involved 45 times, the spleen twice, the ovaries 6 times, the pelvic peritoneum 3 times and the fallopian tubes and the perimetrium each once. In regard to ovarian metastasis he cited the statistics of the Middlesex Hospital, with 4.8 per cent of cases, and of Guy's Hospital, with 8.6 per cent.

A number of individual reports appearing in the literature since 1920 will be mentioned briefly. Sappington<sup>9</sup> in 1922 reported a single case of metastasis to the spleen. Feist and Bauer<sup>10</sup> in 1922 referred to 53 instances. From the description it is not clear whether autopsies were performed. Neither the spleen, the adrenal glands nor the ovaries were mentioned as sites of metastasis. Dial<sup>11</sup> in 1930 reported an individual case in which there was metastasis to the spleen. He stressed the rarity of this occurrence. Leroux and Vermès<sup>12</sup> in 1931 described 3 cases of carcinoma of the breast. In all of these the ovaries were involved; the spleen was involved in 2 and the adrenal glands in 1. Crile<sup>13</sup> in 1931 stated that among 520 mammary carcinomas, metastasis to the ovary was found only once. The spleen was not mentioned. Moiroud<sup>14</sup> in 1932 described a patient in whom the first sign of a metastatic carcinoma of the ovary was an intraperitoneal hemorrhage. The primary carcinoma was in the breast. Essen-Möller<sup>15</sup> in 1933 reported 2

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15. Essen-Möller, E.: *Beobachtungen von Ovarialmetastasen nach Mammakarzinom*, *Acta path. et microbiol. Scandinav.*, 1933, supp. 16, p. 47.

instances of carcinoma of the breast with metastasis to the ovary. He stressed that more metastases would be found in the ovaries if more sections were routinely taken. Scarpitti<sup>16</sup> in 1933 reported an instance of metastatic carcinomas in both ovaries, occurring five years after the primary tumor of the breast had been removed. Simon<sup>17</sup> in 1934 referred to 1 instance, observed by him, in which metastatic carcinomas were found in both ovaries eight years after the patient had been operated on for scirrhus carcinoma of the breast. Warren<sup>18</sup> in 1936 reported a case in which there were diffuse metastases in the spleen, the adrenal glands and both ovaries. This case was published principally because of metastasis in the pineal body. McMenemey<sup>19</sup> in 1937 described a solitary metastasis in the spleen. Foot and Moore<sup>20</sup> in 1938 studied an epidermoid carcinoma of the breast with diffuse metastasis involving the spleen. Larson<sup>21</sup> in 1938 described an instance of metastases to both ovaries and the adrenal glands. Glomset<sup>22</sup> in 1938 stated that of his 43 cancers of the breast, 25 showed metastasis to the adrenal glands. Beham<sup>23</sup> in 1938, citing Shaw and Johnson, stated that metastasis developed in the ovaries in 10 per cent of patients with mammary cancer who came to autopsy. In regard to metastasis to the spleen, Beham stressed that this is very infrequent, occurring in about 2 per cent of the cases in which autopsy is done. However, he emphasized that statistical studies may not give absolutely accurate results, since the entire spleen is not examined microscopically. Held<sup>24</sup> in 1939 reported 3 instances of carcinoma of the breast. In 1 metastases were found to the spleen and ovaries. Grams<sup>25</sup> in 1939 found microscopic intracapillary metastases to the spleen, ovaries and adrenal glands. In the two latter

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16. Scarpitti, C.: Il cancro ovarico metastatico a cancro del seno, *Tumori* **19**: 47, 1933.

17. Simon, S.: Metastatisches Ovarialkarzinoma, *Zentralbl. f. Gynäk.* **58**:356, 1934.

18. Warren, S.: Studies on Tumor Metastasis: Metastasis to the Pineal Gland, *Am. J. Cancer* **28**:713, 1936.

19. McMenemey, W. H.: Solitary Metastasis in Spleen in Carcinoma Simplex of Right Breast with Extensive Local Spread, *Lancet* **1**:691, 1937.

20. Foot, N. C., and Moore, S. W.: A Fatal Case of Deep-Seated Epidermoid Carcinoma of the Breast with Widespread Metastases, *Am. J. Cancer* **34**:226, 1938.

21. Larson, C. P.: Carcinoma of the Breast with Krukenberg-Type Metastasis, *West. J. Surg.* **46**:550, 1938.

22. Glomset, D. A.: Incidence of Metastasis of Malignant Tumors to the Adrenals, *Am. J. Cancer* **32**:57, 1938.

23. Beham, R. J.: Cancer with Special Reference to Cancer of the Breast. St. Louis, C. V. Mosby Company, 1938.

24. Held, E.: Metastases vaginales de cancer du Sein et de l'estomac, *Rev. franç. de gynéc. et d'obst.* **34**:482, 1939.

25. Grams, L. R.: Intracapillary Microscopic Metastatic Mammary Gland Carcinoma of the Lungs and Other Viscera, *Arch. Path.* **28**:865 (Dec.) 1939.

organs the tumor cells also spread into the parenchyma. Bolker and Shapiro<sup>26</sup> in 1940 described an instance of metastasis to the adrenal glands and to many other organs.

Perhaps the most careful study made recently was that of Warren and Witham<sup>3</sup> in 1933. These authors studied 162 tumors (160 carcinomas and 2 sarcomas) of the breast. The adrenal glands were involved 50 times, the spleen 23 times and one or both ovaries 15 times. According to the frequency, the lungs were most commonly involved, followed by the liver, bones, regional lymph nodes, skin, pleura and adrenal glands, in that order.

This brief review of the literature is interesting. Because of the relatively many reports of individual cases or of a few cases of metastases to the spleen or ovary on record, the impression may be gained that involvement of these organs is rare. It is also of interest to compare the reports of larger series of cases. Thus, Crile<sup>13</sup> referred to metastasis in the ovary in a single instance among 510 cases of carcinoma of the breast and did not mention the occurrence of metastases in the spleen, while Warren and Witham<sup>3</sup> found that of 162 cases the ovaries were involved in 15 and the spleen in 23. Taylor<sup>27</sup> remarked that the frequency of metastases of various kinds has received some attention but that the figures vary widely, depending on whether they derive from clinical or autopsy reports.

#### RESULTS

The results are summarized in table 1, which, among other items, shows the type of carcinoma, the interval between operation and death and the sites of metastases. It must be emphasized, however, that because of the limitations of autopsy permits nothing can be said about involvement of the brain, spinal cord and osseous system. The brain was examined only when there were clinical symptoms indicative of its involvement. As a rule, only those bones were examined which could be exposed by the routine method of opening the body.

The distribution of the metastatic lesions is quite evident from this table. Table 2 is included to summarize the findings.

The most common location, as is seen from table 2, is the lungs, which were involved in 28 instances. Next came the liver, involved in 24 instances. The next most common locations were rather surprising. These were the adrenal glands (19 instances); the spleen (10 instances) and the ovaries (7 instances). These figures when compared with those

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26. Bolker, H., and Shapiro, A. L.: Appendiceal Metastasis, *New York State J. Med.* **40**:219, 1940.

27. Taylor, G. W.: Cancer of the Breast, *Internat. Abstr. Surg.* **55**:1, 1932; in *Surg., Gynec. & Obst.*, July 1932.

TABLE 1.—Summary of Results

Metastases to																													
Organs					Lymph Nodes					Bones																			
Patient	Age	Sex	Primary Carcinoma of Breast	Interval Between		Type of Carcinoma	Lungs	Liver	Spleen	Kidney	Adrenal Glands	Ovaries	Axillary	Supraclavicular	Intraclavicular	Mediastinal	Peritoneal	Retroperitoneal	Inguinal	Clavicle	Sternum	Ribs	Spinal Column	Pelvic	Femur	Skull	Other Structures	Post-operative Irradiation	
				Recognition and Operation (Radical Mastectomy)	Operation and Death																								
1	..	F	Left	3 months	5 years	Ductal	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Spinal cord; right breast; skin	+		
2	48	F	Left	1 month	12 years	Scirrhus	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Pleura	+	
3	35	F	Left	No data	9 months	Terminal ducts and acini	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Pleura	..	
4	42	F	Right	Not operated on, present for 3 years	11 months	Ductal	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Pleura; pericardium	..	
5	51	F	Left	8 months	9 years	Ductal	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Brain	+	
6	45	F	Left	No data	2½ years	Ductal	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Skin; pericardium; pleura	+	
7	32	F	Left	No data	7 years	Ductal	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Right breast	..	
8	62	F	Left	No data	2 yr. 9 mo.	Papilliferous cystadenocarcinoma	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Thyroid; myocardium; intercostal muscles; gastro-intestinal tract; uterus; cervix; pericardium; pleura	+	
9	36	F	Right	1 month	16 years	Medullary	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Right breast	..	
10	57	F	Left	6 months	3 months	Ductal	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
11	50	F	Left	No data	8 months	Anaplastic adenocarcinoma	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12	22	F	Left	No data			..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
13	57	F	Right	6 months	6 months	Ductal	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Stomach; peritoneum; trachea	+	
14	35	F	Right	No data	1 month	Mucinous (signet ring)	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Pleura	..	
15	46	F	Right	No data	6 years	Medullary	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Pleura; pericardium	+	
16	63	M	Left	No data	2 years	Anaplastic adenocarcinoma	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	Right breast; scalp; brain; pericardium; pancreas; gallbladder	..	
17	57	F	Right	5 years	4 years	Ductal	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
18	78	F	Right	No data	7 years	Papilliferous cystadenocarcinoma	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
19	30	F	Left	.....	5 years	Scirrhus	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
20	60	F	Right	No data	24 years	Adenocarcinoma	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
21	53	F	Left	No data	10 months	Ductal	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

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in the older publication of Paget<sup>5</sup> (735 cases; spleen involved in 17, adrenal glands in 30, ovary apparently in none), of Williams<sup>6</sup> (44 cases; spleen involved in 1, adrenal glands in 2, ovary apparently in none) or of Gross<sup>2</sup> (114 cases; spleen involved in 5, adrenal gland in 1, ovary in 3) are exceptionally high. However, even in 1922 Handley<sup>8</sup> found that of 53 cases the spleen was involved in only 2 and the ovaries in 6; he did not mention the adrenal glands as locations of metastases. Earlier (1906) he<sup>28</sup> listed the frequency of ovarian metastases as 5.6 per cent. As a matter of interest it must be pointed out that in the current relevant

TABLE 2.—*Frequency of Metastases in Various Organs and Structures*

Organs Involved	No. of Cases		No. of Cases
Lungs.....	28	Bones †	
Liver.....	24	Clavicle.....	1
Spleen.....	10	Sternum.....	4
Kidneys.....	6	Ribs.....	7
Adrenals.....	19	Spinal column.....	11
Pancreas.....	5	Femur.....	3
Ovaries.....	7	Pelvis.....	7
Opposite breast.....	5	Skull.....	3
Cerebrum *.....	4		
Spinal cord *.....	1	Unusual Locations	
Diaphragm.....	6	Broad ligament.....	1
Pericardium.....	9	Uterus.....	2
Pleura.....	10	Cervix.....	2
Peritoneum.....	4	Pouch of Douglas.....	1
		Intestinal wall.....	1
Lymph Nodes		Gallbladder.....	2
Axillary.....	12	Superior vena cava.....	2
Supraclavicular.....	3	Thyroid.....	1
Infraclavicular.....	2	Myocardium.....	1
Mediastinal.....	13	Gastrointestinal tract.....	3
Peritoneal.....	11	Trachea.....	1
	13	Hypopharynx.....	1
	3	Intercostal muscles.....	1
		Scalp.....	1
		Skin.....	2

\* The brain and spinal cord were examined only when there were clinical symptoms referable to their involvement.

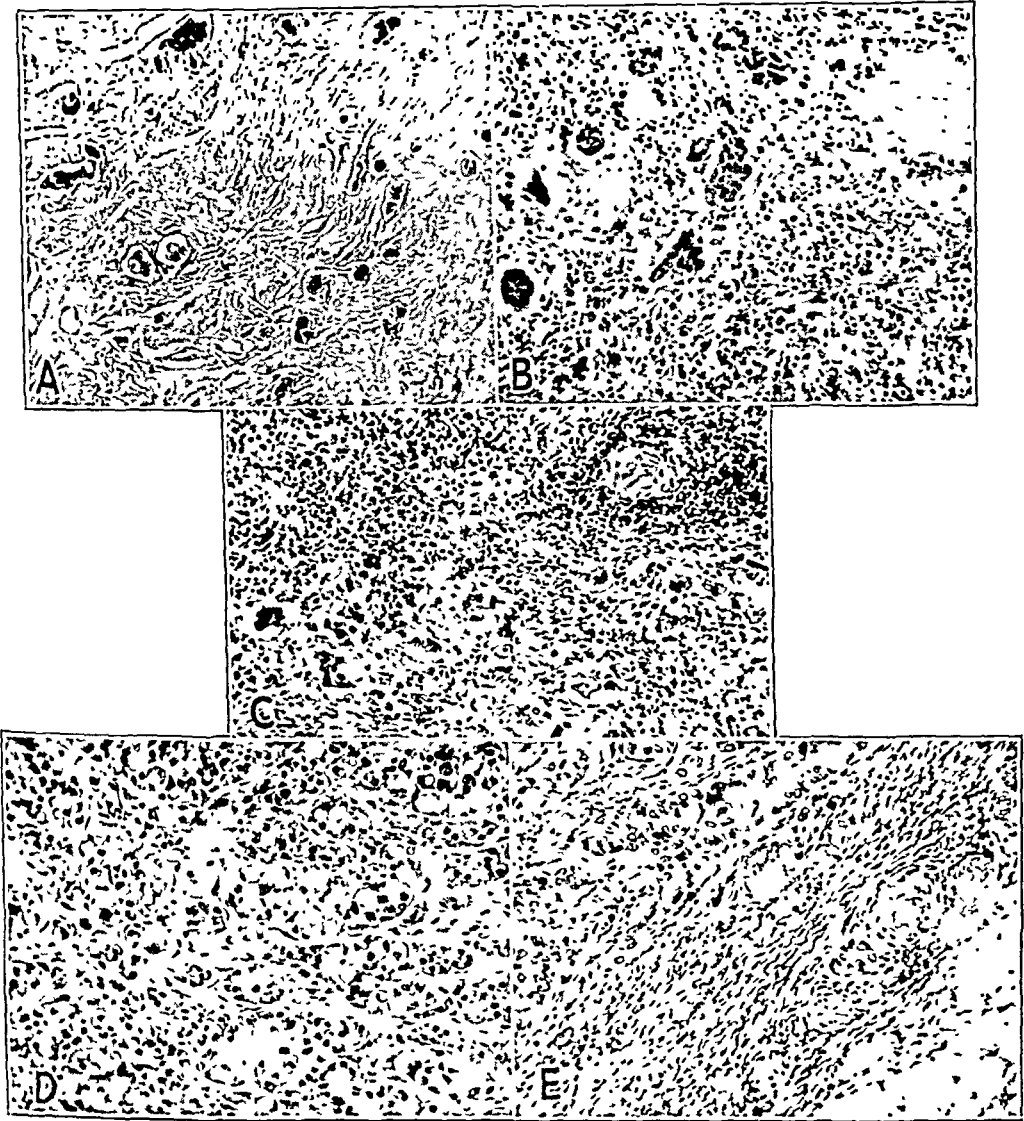
† As a rule, only those bones were examined that could be made visible by the routine method of opening the body.

textbooks, as a rule, only these older authorities are cited. Only the figures obtained by Warren and Witham<sup>3</sup> (1933) correspond somewhat to ours. In their series of 162 tumors (160 carcinomas and 2 sarcomas) the spleen was involved in 23 instances, the adrenals in 50 and the ovaries in 15. The figures may be expressed in percentage and compared with those in our series, thus: In Warren and Witham's series the spleen was involved in 14.4 per cent of their cases, the adrenals in 31.25 per cent and the ovaries in 9.3 per cent, and in our series the spleen contained metastases in 23.3 per cent, the adrenals in 41.2 per cent, and the ovaries in 16.3 per cent. The percentages are used here only for comparison with the values obtained in Warren and Witham's studies. We are well

28. Handley, W. S.: *Cancer of the Breast and Its Operative Treatment*, London, J. Murray, 1906.



aware that figures expressed in percentage may give an erroneous conception if used for the relatively small number of cases on which this study is based.



*A*, primary ductal carcinoma of the breast. Note the individual tumor cells within dense fibrous stroma (scirrhous carcinoma). Hematoxylin and eosin preparation;  $\times 110$ . *B*, metastasis to the spleen. Note the individual groups of tumor cells. Hematoxylin and eosin preparation,  $\times 150$ . *C*, metastasis to the spleen. Note the few isolated tumor cells and groups of tumor cells. Iron hematoxylin and eosin preparation;  $\times 110$ . *D*, metastasis of mucinous carcinoma to the adrenal gland (signet ring cell variety). Iron hematoxylin and eosin preparation,  $\times 110$ . *E*, metastasis of carcinoma to the ovary. Note the corpus albicans at the right lower portion of the picture and the carcinoma cells in the left upper half. Iron hematoxylin and eosin preparation,  $\times 110$ .

As far as the spleen is concerned, the high incidence of splenic metastases may perhaps have been due to the fact that in this series a careful histologic examination was made of all the organs. However, in only 3 instances was the tumor detected in the spleen solely on microscopic examination, and in the 7 other instances it was recognized grossly. In the latter the tumors either were seen in the form of several grayish yellow nodules varying in diameter from 0.2 to 1.6 cm. (6 cases) or manifested themselves as minute translucent areas, not exceeding 0.1 or 0.2 cm. in diameter, scattered diffusely throughout the organ (1 case). Dial<sup>11</sup> in 1930 reported a single case of carcinoma of the breast with metastasis to the spleen and stressed the rarity of its occurrence. The gross detection of carcinoma metastases in 7 of 10 cases compares with the findings of Warren and Davis,<sup>29</sup> who recognized splenic metastases grossly in over half of their 46 cases of metastases to the spleen from various primary carcinomas.

Sappington,<sup>9</sup> in discussing an instance of carcinoma of the breast with metastasis to the spleen, stated that carcinoma of the spleen secondary to cancer of the breast was present as part of generalized microscopic carcinomatosis. He further stated that the rarity of cancer of the spleen is genuine but that there is evidence to show that there is actually no local immunity and that microscopic examination may add considerably to the number of reported cases. He quoted a letter of Ewing's concerning splenic metastases as follows: "I do not remember an extensive infiltration of the spleen in mammary cancer, but this organ is sometimes the seat of bulky metastases from other epithelial growths. The largest I have seen were in ovarian adenocarcinoma and melanoma. I know of no summary of the literature on splenic metastases of carcinoma, while most of the references mention the comparative immunity of this organ, which on the whole is rather striking." Also a letter of F. B. Mallory is quoted: "In the last twenty-five years, we have had 4,265 necropsies. There have been cancer metastases (of the spleen) ten times. That is a little oftener, probably, than you would have imagined." It is interesting to compare these statements with Warren and Witham's<sup>3</sup> data and with ours. Because of their figures, Warren and Witham remarked that this frequent involvement of the spleen lends little credence to the assumed resistance of the spleen to the development of cancer. From our studies we are in full agreement with this statement. In a later study, Warren and Davis<sup>29</sup> reported metastases to the spleen in 28 of 193 instances of carcinoma arising in the breast.

In comparing the various primary carcinomas throughout the body in relation to the frequency of metastases to the spleen, it is of interest

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29. Warren, S., and Davis, H.: Studies on Tumor Metastases: The Metastasis of Carcinoma to the Spleen, *Am. J. Cancer* **21**:517, 1934.

to note that Yokohata<sup>30</sup> reported 10 instances of splenic metastasis. In 4 of these the deposits were from primary carcinomas of the stomach; in 2, from carcinomas of the bronchus, and in 1 each, from carcinomas of the breast, gallbladder, rectum and ovary respectively. Warren and Davis<sup>29</sup> stated that among 1,140 autopsies on patients with carcinoma, metastatic carcinoma to the spleen was found in 46 or 4 per cent; 28 of the tumors were primary in the breast. Willis<sup>31</sup> pointed out that metastases to the spleen occurred in 4 per cent of cases of malignant tumor. Krumbhaar<sup>32</sup> found among 17,500 incompletely studied autopsies 38 instances of secondary carcinoma of the spleen. Nine of these were primary mammary cancers. Among 6,500 carefully studied autopsies, there were 21 cases of carcinoma metastatic to the spleen, in 7 of which the tumors were primary mammary cancers. He stated that the greater frequency of splenic metastases from carcinoma of the breast has been recognized even in textbooks.

In this series the ovaries were involved 7 times. In 4 instances both ovaries contained metastases; in 3, the right ovary alone. The tumors were all recognized grossly. In 2 patients (cases 14 and 34) in whom both ovaries were involved, these organs were uniformly considerably enlarged, measuring 7 by 7 by 7 cm. and 8 by 9 by 10 cm. respectively in their greatest dimensions. In both instances it was first thought that the primary tumor was in the ovaries. It may be of special interest to point out that in both of these cases the primary carcinoma was of a special mucinous type and that the ovarian tumor consisted practically entirely of signet ring tumor cells (to be mentioned later).

Bland-Sutton<sup>33</sup> studied metastatic carcinomas of the ovaries. He stated that such tumors are found with 10 per cent of primary carcinomas of the breast and of the stomach. He also reported 1 specific instance in which the ovarian metastases were found in a 42 year old woman seven years after the primary mammary carcinoma had been removed. Willis<sup>31</sup> stressed that in 3 per cent of cases of malignant tumor the ovaries are the seat of metastases. Scarpitti<sup>10</sup> stated that of 37 metastatic cancers in the ovary observed at Peham's Clinic 2 were primary in the breast. This author also reported an instance observed by him in which metastasis occurred in both ovaries five years after the primary tumor had been removed. Other individual instances have been mentioned.

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30. Yokohata, T.: Ueber die mikroskopischen Krebsmetastasen in der Milz, *Ztschr. f. Krebsforsch.* **25**:32, 1927.

31. Willis, R. A.: *The Spread of Tumors in the Human Body*, London, J. & A. Churchill, 1934.

32. Krumbhaar, E. B.: *The Incidence and Nature of Splenic Neoplasms*, *Ann. Clin. Med.* **5**:833, 1927.

33. Bland-Sutton, J.: *Secondary (Metastatic) Carcinoma of the Ovaries*, *Brit. M. J.* **1**:1216, 1906.

Taylor's<sup>34</sup> remark, in abstracting a pertinent report, that ovarian metastases are not as rare as the published records would indicate, is apparently quite correct, at least as far as our series would indicate.

There are instances on record of primary carcinomas of the ovary with metastasis to the breast (Ewing<sup>1</sup>). From our experience it seems that one must be extremely careful to rule out a primary cancer of the breast with ovarian metastases. As has been stated, in 2 cases in this series the large ovarian tumors were first thought to be the primary cancers. In the first (case 14) a radical mastectomy had been performed six months before the patient died, and in the second (case 34) the tumor of the breast was not observed by the patient, a Negress 49 years old who had continuous vaginal bleeding. The mammary tumor was recognized on her admission to the hospital, but she died shortly thereafter.

The adrenal glands were involved in 19 instances. In 13 instances the tumors were recognized grossly, in the form of seemingly well circumscribed nodes not exceeding 1 cm. in their greatest dimension. Both adrenal glands were grossly involved in 7 instances, the right alone in 3 and the left alone in 3. Microscopic metastases were recognized in 6 instances. Most commonly these tumors involved the medulla.

Though there are not many systematic studies of mammary cancers on record indicating the adrenal glands as locations for metastatic growth, there are a number of studies available on metastases to the adrenal glands from various primary tumors. Willis<sup>31</sup> stated that of 27 metastatic carcinomas in the adrenal glands 7 were primary in the breast. Of 42 metastatic tumors recorded by Clark and Rowntree,<sup>35</sup> 8 were primary in the breast. As a matter of fact, carcinoma of the breast more commonly produced metastases in the adrenal glands than did any other one tumor. Glomset<sup>22</sup> reported the incidence of metastases to these glands as 13 per cent of 821 malignant tumors. There were 43 carcinomas of the breast in this series 25 of which had produced metastases to the adrenal glands.

From our observations and the few reports available in the literature, it seems clear that metastasis to the adrenal glands is by no means rare. In our series the adrenal gland, with metastases in 19 instances, was the third most frequently involved organ. However, because of the small size of the metastases, these were not recognized clinically.

In regard to the location of metastases in organs other than the spleen, ovaries and adrenal glands, it can be stated that most organs may be

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34. Taylor, H. C.: Note after abstract of Moiroud,<sup>14</sup> *Am. J. Cancer* **17**:854, 1933.

35. Clark, J. H., and Rowntree, L. J.: *Adrenal Gland in Health and Disease*, *Endocrinology* **18**:256, 1934.

involved. The bones, as they were examined through the routine autopsy incision, were often involved. The frequency with which the individual bones were affected is given in table 2.

In 3 of 43 patients (cases 22, 28 and 38) no metastases were found. It is interesting that 1 of these patients (case 28) had had the tumor for thirty-three years without having been operated on, though radiation had been applied during the last few months. When the patient was admitted to the hospital, the tumor was found to be inoperable. In 8 of Warren and Witham's series of 162 cases of malignant tumor of the breast, metastases were not found at autopsy.

Table 1 also shows the period of survival after the operation. In most instances this period was rather short, though in several it was greater than five years. One patient (case 20) lived twenty-four years after radical mastectomy. At autopsy metastases were found in the lungs and in the pleura. Another patient, who showed no evidence of metastases for sixteen years (case 10), died with involvement of the opposite breast and metastases to the lungs. It is interesting to note in this connection that in 5 patients (cases 2, 6, 10, 19 and 40) the opposite breast was also involved. For 4 patients the interval between removal of the carcinoma of the breast and appearance of the tumor in the opposite breast was about five years (case 19), nine years (case 6), twelve years (case 2) and sixteen years (case 10), respectively. The long interval between the appearance of the two carcinomas at first makes it seem possible that the second carcinoma might have been another primary tumor. Yet the histologic similarity of the two tumors speaks for the metastatic nature of the carcinoma in the opposite breast. However, it seems clear that a primary tumor in the opposite breast cannot be ruled out.

The fate of those patients in this series who did not receive radiation treatment as compared with that of the patients treated by irradiation indicates that this treatment was apparently, as far as metastases were concerned, of no avail. However, this series is much too small to allow a definite conclusion in this respect. Furthermore, because of the very nature of this material, the types of carcinomas represented were in many instances the most malignant mammary carcinomas, which had produced widespread metastases and had caused the death of the patients. For this reason, too, no general conclusion can be drawn in regard to the failure of radiation therapy.

It is significant that there were a few patients in this series who were observed clinically for various lengths of time and who had small primary tumors which were recognized neither by the patients nor by the physician. One of these (case 29) was a physician's mother, who had been carefully observed on several occasions; the clinical diag-

nosis was severe anemia and bronchopneumonia. Autopsy showed a small carcinoma of the right breast, measuring 2 by 2 cm. in its greatest dimensions, with principal metastases to the lungs, liver, spleen, kidneys, lumbar vertebrae and hypopharynx. Microscopically this was a ductal carcinoma with mucinous carcinomatous features. In another instance (case 39) the clinical diagnosis was hypertrophic cirrhosis of the liver and chronic rheumatic arthritis. Autopsy disclosed a small carcinoma in the right breast, with principal metastases to the lungs, liver, spleen, adrenals and sternum. Histologically this tumor was a medullary carcinoma. In another patient (case 34), who came to the hospital because of vaginal hemorrhages, a tumor was detected in the left breast which had not been noted by the patient. She died before any treatment could be instituted. At autopsy a carcinoma was found in the left breast, measuring 4 by 5 by 5 cm. in its greatest dimensions, with principal metastases to the lungs, pericardium, intestinal wall, adrenals, ovaries and spinal column. Histologically this was a mucinous carcinoma with signet ring cells, to be described. A fourth patient (case 4) had noted progressive loss of weight, and in the past month the abdomen had grown steadily larger. Blood had not been noted in the feces. The patient, who was in the hospital only twenty-four hours before she died, was thought to have had a gastric or an intestinal malignant tumor. Autopsy revealed a primary carcinoma of the left breast, with principal metastases to the liver, adrenal, pancreas and brain. Histologically the primary tumor was a ductal carcinoma.

These instances are significant because they clearly demonstrate again the known fact that a small or unnoticed carcinoma of the breast may give rise to diffuse metastases. They also emphasize the importance of palpating the breasts carefully during general physical examination. The fact that 2 of these carcinomas showed mucinous features is interesting and brings to one's mind the statement of Cheatele and Cutler<sup>36</sup> that 5 of the 10 mucinous carcinomas observed by them were among the most malignant that can be encountered in the breast.

Table 1 also shows the histologic type of carcinoma. From this study it seems that no one type of carcinoma per se is more malignant than another type. An anaplastic adenocarcinoma in a 22 year old woman (case 12) showed metastases in almost every organ and structure in the body. The patient survived operation only eight months. This recalls Greenough's<sup>37</sup> statement that an adenomatous tumor was one of the most malignant that he had seen. On the other hand, however, a histologically similar tumor in a 60 year old woman (case 20)

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36. Cheatele, G. L., and Cutler, M.: *Tumours of the Breast*, Philadelphia, J. B. Lippincott Company, 1931.

37. Greenough, R. B.: *Varying Degrees of Malignancy in Cancer of the Breast*, *J. Cancer Research* 9:453, 1925.

who lived twenty-four years after radical mastectomy showed distinctly fewer metastases. It is of course likely, from this instance, that the youth of 1 of these patients was one factor that led to the early dissemination of the tumor. However, there are other instances in this series which do not bear out the age factor as contributory either to rapid dissemination of the tumor or to retardation of metastasis.

There were 3 papilliferous cystadenocarcinomas in this series. In a 70 year old patient (case 28), the tumor locally invaded the entire chest wall and was inoperable but showed no metastasis. Another patient (case 18), 78 years old, with a similar carcinoma, lived seven years after radical mastectomy and died with metastases to the pleura, pericardium and mediastinal nodes. Another patient (case 9), aged 36, died with diffuse metastases. Yet histologically the 3 tumors were identical, and their grading would not have aided in determining the prognosis for these patients or helped in predicting the occurrence or nonoccurrence of metastasis. Here, too, the differences in age may be taken into consideration.

The most common type of carcinoma was the ductal carcinoma. Tumors of this type, too, were histologically similar in the various instances but varied widely in regard to the survival of the individual patient and the number of metastases. In this respect one must emphasize Warren and Witham's<sup>3</sup> statement that so far as distribution of metastases is concerned there is little evidence of correlation between the histologic appearance and the extent of metastasis. However, it should be made clear that the markedly anaplastic carcinoma of the breast with numerous atypical mitotic figures certainly is the one which is most likely to produce widespread metastases, regardless of what type of carcinoma it is. On the other hand, it is of great importance for the surgeon and the pathologist to remember the results of Reimann's<sup>38</sup> study, which brought out that an attempt to grade the relative malignancy of 100 cancers of the breast from the histologic pictures of specimens obtained at operation gave false results, as determined by the later history of the patients.

Five carcinomas (cases 14, 29, 34, 36 and 43) may be classified as mucinous carcinomas of the breast. This type of tumor was studied recently by one of us<sup>39</sup> and classified into true mucinous carcinoma, ductal carcinoma with mucinous features, and the signet ring cell mucinous carcinoma. All of these 5 carcinomas had produced widespread metastases. However, none of the 5 could be classified as a true mucinous carcinoma, consisting entirely of ductal or cystic structures

38. Reimann, S. P.: The Issues at Stake in the Grading of Tumors, *Arch. Path.* 8:803 (Nov.) 1929.

39. Saphir, O.: Mucinous Carcinoma of the Breast, *Surg., Gynec. & Obst.* 72:908, 1941.

filled with mucinous material, without the presence of other tumor elements. Three of these 5 tumors (cases 29, 36 and 43) were ductal carcinomas with mucinous features, and 2 were signet ring cell mucinous carcinomas (cases 14 and 34), characterized histologically by well preserved mucin-secreting epithelial cells with basophilic or clear cytoplasm and crescent-shaped, compressed nuclei situated at the bases of the cells.

From the histologic study of this series of carcinomas of the breast it is clear that it is definitely not the type of carcinoma which is responsible for the shorter or longer survival period of the patient or for the appearance, spread and number of metastases. However, it was found, especially with ductal carcinomas and adenocarcinomas, that whenever the continuity of the lining cells of the glandular structures was interrupted or (as in ductal carcinomas) the integrity of islands of tumor cells was disturbed and individual, isolated tumor cells began to invade the surrounding breast tissue, this phenomenon constituting the most definite sign of a high degree of malignancy. Isolated tumor cells exhibiting severe anaplasia, separated from primary basic structures of the individual carcinoma and singly or in small groups invading neighboring regions, must be considered the most important factor. Most of the tumors which produced metastases in the spleen, ovaries and adrenal glands showed an infiltration of isolated carcinoma cells outside the primary tumor. This was especially true for the mucinous carcinoma of the signet ring cell variety.

#### SUMMARY

The sites of metastases of 43 carcinomas of the breast are given. Special emphasis is placed on the occurrence of metastasis to the spleen, adrenal glands and ovaries, each of which organs was submitted to a microscopic study. The spleen was involved in 10 instances; the adrenal glands in 19, and the ovaries in 7. Most commonly the metastatic tumors were recognized grossly. No metastases were found in 3 instances. From the microscopic appearance of the primary tumor no conclusion could be drawn as to the period of survival of the patients or the number of metastases found at autopsy. However, the presence of isolated tumor cells, regardless of the type of carcinoma, separated from primary basic structures of the carcinoma, indicates a high degree of malignancy. Carcinomas consisting of such isolated and diffusely infiltrating tumor cells were often those which produced metastases in the spleen, adrenal glands and ovaries. Emphasis is placed on the occasional small and clinically unnoticed carcinoma which may give rise to widespread metastases. In this small series there was no apparent difference in the survival of patients given postoperative radiation treatment and of those to whom no such therapy was administered.



# EFFECTS OF UNCOMPLICATED HEMOCONCENTRATION (ERYTHROCYTOSIS)

WITH PARTICULAR REFERENCE TO SHOCK

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An increase in the concentration of the red blood corpuscles occurs in many abnormal conditions, notably in secondary shock. The hemoconcentration associated with secondary shock results from the loss of plasma, local or diffuse or both. This results in a reduction in the circulating blood volume. The total number of circulating erythrocytes in the absence of gross injury remains constant or is moderately increased, depending on the discharge of cells from the splenic reservoir.

As has been stated, hemoconcentration is usually accompanied with a decrease in the blood volume, and it is difficult if not impossible to assess the roles exercised by each of these two factors in the resulting alterations. The purpose of the present experiments was to determine the effects of hemoconcentration, uncomplicated as far as possible by alterations in the blood pressure and blood volume, on the general condition of the animal and the appearance of the tissues.

## METHODS

The method for producing hemoconcentration consisted of removing whole blood and replacing this with an equal volume of red blood corpuscles. Centrifugation was used for separation of the cells and the plasma. Only enough plasma was left with the cells to permit the introduction of the latter through a needle. Clotting was prevented by the use of sodium citrate. Some of the cells were obtained from the blood removed from the experimental animal, and the additional ones necessary to bring the volume up to that of the whole blood removed were obtained from compatible donors. Care was taken to reduce the trauma to the blood to a minimum.

A total of 21 experiments were performed on dogs. Some of the animals were given water, meat and chow, and the others were allowed only dry chow. As no pain was experienced, anesthetics were not used in any of the experiments.

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Whole blood was removed and corpuscles were replaced once daily. This daily removal and replacement varied slightly but usually equaled approximately 2 per cent of the body weight, or one fifth of the total blood volume. Occasionally the volume of corpuscles reintroduced was in excess of the whole blood removed. The elapsed time between the bleeding and the reintroduction of corpuscles varied from five to thirty minutes. Rigid asepsis was observed in some of the studies, and in the remaining ones the syringes, needles and other supplies were washed carefully and boiled frequently.

Studies on the animals included determinations of the pulse and respiratory rates, mean blood pressure, hematocrit readings and red blood cell counts. In addition, white blood cell counts and determination of the values for nonprotein nitrogen and for serum chloride were performed in some experiments. In the hematocrit determinations, the Van Allen tubes which contained the blood were centrifuged 2,700 revolutions per minute for fifteen minutes.

Most of the animals were killed at varying intervals, depending on the degree of hemoconcentration and the animal's condition. The aim in most experiments was to obtain the most marked degree of hemoconcentration that appeared to be compatible with the well-being of the animal. We were not always successful in this respect, and some of the animals became very ill and died.

When it was decided that the observations should be terminated, which was usually after about eight days, death was caused by rapid decapitation. A careful autopsy was performed, and the tissues removed for microscopic study included the brain, lung, heart, liver, duodenum, pancreas, adrenal, kidney, ileum and spleen.

## RESULTS

There was a fairly marked individual variation among the animals in the ease with which hemoconcentration could be produced. High concentrations of red blood corpuscles could be readily attained in most experiments without the appearance of shock. This increase in concentration occurred earlier in the animals deprived of water.

In a number of instances the animal was apparently normal to outward appearances, despite a high degree of concentration, at the time it was killed. It was observed in other instances that a dog would appear to be in fairly good condition at a given level of concentration of red corpuscles and that a relatively small increase in concentration would seem to precipitate a disastrous chain of symptoms and signs. The point at which this change occurred was somewhat variable, but it usually appeared when the hematocrit reading was approximately 70 per cent and the red blood cell count approximately 10,000,000 per cubic millimeter. The duration as well as the degree of the hemoconcentration appeared to be a factor in determining the condition of the animal. If the increase in concentration was maintained at a high level, untoward symptoms consisted of loss of appetite, lethargy and muscular weakness. Weakness and muscular incoordination became so marked that the animals could scarcely stand unsupported. Terminally, the dogs passed into a coma lasting from hours to several days. Several dogs exhibited clonic convulsions for a number of hours preceding death.

# *Effects of Plasmapheresis (Constant Volume, Food and Water Allowed)*

Dog No.	Studies *	Control Observations	Days Following Control Observations—Plasmapheresis Daily											Comment
			1	2	3	4	5	6	7	8	9	10	11	
1 Weight 7.5 Kg.	Blood pressure.....	108	122	123	128	133	138	...	133	138	132	116	...	Appeared to be in good condition on tenth day; killed; no gross abnormalities
	Pulse.....	102	110	94	78	120	94	...	110	104	102	102	...	
	Respiration.....	16	24	36	16	Panting	52	...	Panting	Panting	61	78	...	
	Temperature.....	102.8	101.4	101.8	100.1	102.3	101.8	...	102.3	102	102.6	101.2	...	
	Hematocrit.....	50.0	50.5	56.0	56.0	61.8	68.5	...	66.4	64	70.3	78	...	
	Red blood cell count.....	6,780,000	7,460,000	8,010,000	8,240,000	9,460,000	10,700	...	8,400,000	9,140,000	9,830,000	10,320,000	...	
	White blood cell count.....	12,000	8,650	7,550	7,800	10,750	10,700	...	12,000	22,500	16,250	27,700	...	
	Nonprotein nitrogen.....	46	...	32	...	...	...	...	46	...	...	56	...	
	Sodium chloride.....	124	...	104	...	...	...	...	101	100	...	113	...	
	Blood removed.....	100	100	150	200	200	200	...	100	100	50	...	...	
	Cells injected.....	100	110	200	200	200	200	...	150	200	150	...	...	
2 Weight 9.5 Kg.	Blood pressure.....	128	143	138	143	133	133	...	153	133	133	139	...	Dog slightly weak but condition not bad on tenth day; killed; slight congestion
	Pulse.....	104	106	108	120	100	92	...	106	74	68	68	...	
	Respiration.....	40	42	60	Panting	Panting	26	...	32	Panting	32.1	30	...	
	Temperature.....	102.6	102	101.8	102	102.2	101.8	...	101.2	102.3	102.1	101.4	...	
	Hematocrit.....	46.5	50	54.8	60	59.4	61.5	...	72.3	74.6	72.3	83.0	...	
	Red blood cell count.....	5,700,000	7,380,000	7,670,000	7,580,000	8,450,000	7,850	...	11,140,000	12,340,000	10,860,000	11,210,000	...	
	White blood cell count.....	16,000	20,350	15,960	6,850	12,300	7,850	...	7,030	27,200	21,350	17,350	...	
	Nonprotein nitrogen.....	37	...	36	...	...	...	...	36	...	...	61	...	
	Sodium chloride.....	113	...	101	...	...	...	...	101	...	...	113	...	
	Blood removed.....	100	150	200	200	200	200	...	100	...	...	...	...	
	Cells injected.....	100	150	200	200	200	200	...	200	100	100	...	...	
3 Weight 11 Kg.	Blood pressure.....	138	133	128	123	123	133	...	133	123	108	109	104	Slightly weak; otherwise well on eleventh day; 100.2 killed; slight congestion
	Pulse.....	72	102	88	80	74	136	...	112	114	86	100	106	
	Respiration.....	34	24	18	42	40	42	...	Panting	Panting	Panting	20	22	
	Temperature.....	103.4	102.1	101.3	101.2	102.2	103	...	103.1	102.9	104.4	102.6	100.2	
	Hematocrit.....	43.2	43.8	47.5	53.5	57	54.7	...	59.2	57	62	77.5	69.2	
	Red blood cell count.....	4,760,000	5,660,000	7,540,000	8,230,000	8,570,000	8,020,000	...	8,960,000	9,030,000	9,420,000	11,040,000	10,810,000	
	White blood cell count.....	11,800	7,550	8,550	9,930	23,300	14,600	...	22,280	38,400	36,200	33,400	18,350	
	Nonprotein nitrogen.....	56	...	32	...	...	...	...	38	...	...	43	...	
	Sodium chloride.....	116	...	99	...	...	...	...	103	...	...	107	...	
	Blood removed.....	100	175	150	200	150	200	...	153	100	...	...	...	
	Cells injected.....	100	225	150	200	150	200	...	200	200	100	...	...	
4 Weight 9.5 Kg.	Blood pressure.....	118	108	103	103	113	...	...	103	88	91	...	...	Very ill on ninth day; continuous convulsive seizures; killed; much engorgement and some congestion and hemorrhage
	Pulse.....	96	118	98	84	76	...	...	80	62	60	...	...	
	Respiration.....	18	24	23	36	24	...	Panting	102.4	101.0	102.6	100.8	...	
	Temperature.....	101.9	102	100.2	102.4	101.7	...	...	59.6	62.5	65.5	80	...	
	Hematocrit.....	40.1	49.0	55.5	55.0	53.5	...	...	8,400,000	8,700,000	9,080,000	10,550,000	...	
	Red blood cell count.....	5,980,000	7,240,000	8,120,000	8,500,000	7,830,000	...	...	21,500	22,200	28,550	29,250	...	
	White blood cell count.....	16,300	16,450	12,000	12,000	4,250	...	...	62	...	90	...	...	
	Nonprotein nitrogen.....	38	...	34	...	...	...	...	...	...	...	...	...	
	Sodium chloride.....	116	...	93	...	...	...	...	101	...	121	...	...	
	Blood removed.....	150	150	200	200	150	...	...	100	100	...	...	...	
	Cells injected.....	175	150	200	200	200	...	...	200	200	...	...	...	

\* Mean blood pressure in millimeters of mercury; pulse and respiratory rates, per minute; temperature, degrees Fahrenheit; nonprotein nitrogen, milligrams per hundred cubic centimeters; sodium chloride, milliequivalents per liter; the amounts of blood removed and injected are expressed in cubic centimeters.

However, as stated previously, marked degrees of hemoconcentration were produced in most of the experiments without the development of untoward symptoms. The accompanying table contains the results of representative experiments. The animal in experiment 1 was in excellent condition despite a hematocrit reading of 78; those in experiments 2 and 3 appeared well except for slight weakness, the hematocrit readings being 69 and 83, while the animal in experiment 4 was very ill, the hematocrit reading being 80.

The animals which appeared to be in good general condition despite the hemoconcentration presented no gross abnormalities except for moderate vascular engorgement on postmortem examination. Similarly, microscopic examination revealed vascular engorgement. A small amount of hemorrhage was noted in a few of the sections, but this was not marked. The duodenum of 1 of the animals showed a small amount of necrosis, but this was the exception rather than the rule. There was an accumulation of polymorphonuclear leukocytes in some of the tissues, but these cells were mainly in the vessels and appeared to be the result of stagnation rather than exudation. In general, the tissues appeared remarkably normal except for the vascular engorgement which was to be expected.

The abnormalities in the animals which were extremely ill or which died were considerably more marked. Gross hemorrhage was apparent in some of the tissues. Microscopic examination revealed marked vascular engorgement, hemorrhage, mild degrees of necrosis and leukocytic infiltration. The alterations were most marked in the duodenum, adrenal and liver. The tissues of the animals which had not been allowed water were less moist than were those of the others. Several of the ill animals had acute peptic ulcers. Rather marked fatty metamorphosis of the liver was observed in 2 dogs.

#### ADDITIONAL OBSERVATIONS

Two additional types of experiments were performed. The main purpose of these experiments was to determine whether hemoconcentration produced in other ways would be associated with alterations in the tissues. Since the previous studies had shown minimal changes except for vascular engorgement (unless the animals were moribund), these additional observations are of little value. They serve, however, to some extent as a check on the other studies. The two types of experiments were as follows: (1) water deprivation alone, in which the animals were maintained without water but were allowed dried dog chow as desired, and (2) "reduced volume" plasmapheresis experiments, in contrast to the "constant volume" ones that have been described, in which the dogs not only were deprived of water but were subjected to plasmapheresis in which only their own cells were reintroduced, there

being each time a reduction in the total blood volume equal to the quantity of plasma removed. By allowing sufficient time between each two plasmaphereses for the reduction in the blood volume to be compensated for in part or in whole, evidences of shock could usually but not always be avoided.

There were 3 experiments in which the effects of simple dehydration were studied. The greatest increase in the hematocrit reading was from 41 to 61 per cent. In the 2 experiments which were terminated at five and eight days respectively, no definite pathologic changes were noted on study of the tissues. In the remaining experiment, in which the animal died at the end of twenty-one days, bronchopneumonia was the outstanding pathologic condition observed.

There were 7 experiments with plasmapheresis combined with water deprivation in which the animals' own corpuscles but not donor ones were reintroduced. The greatest increase in the concentration of the red blood cells was from 40 to 63 per cent. A more marked increase in the concentration could not be produced in this type of experiment without the development of shock, probably as a result of the diminution in the plasma and blood volumes. Excluding the studies on very sick animals, most of the tissues appeared essentially normal. Moderate polymorphonuclear infiltration of the adrenal cortex was observed in 1 experiment.

#### COMMENT

If most of the animals with significant increases in the concentration of erythrocytes had become ill and if the examination had revealed marked changes in the tissues, the possibility would have arisen that the alterations might be due to trauma to the blood in the process of separating plasma from cells, to incompatible blood or to infection. As has been stated, the alterations were not marked except in the very ill animals. Furthermore, the blood was handled with care; attempts were made to avoid infection, and compatibility tests were performed.

In the light of previous observations, it is not surprising that the tissues of the moribund animals showed such changes as hemorrhage and early necrosis. One of us (A. B.<sup>1</sup>) found that the removal of blood in small amounts at frequent intervals from unanesthetized animals in such a manner that the blood pressure is at a low level for a couple of hours before death results in capillary congestion and hemorrhage and in early necrosis of the cells of some of the organs. Hemorrhage into the lumen of the intestinal tract occurred in some experiments. Hemoconcentration of significant degrees was not a factor in these previous studies.

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1. Blalock, A.: Shock: Further Studies with Particular Reference to the Effects of Hemorrhage, *Arch. Surg.* 29:837 (Nov.) 1934.

In view of the relation of viscosity to corpuscular volume, it is rather surprising that severe degrees of hemoconcentration are tolerated as well as they are. Poiseuille showed that the rate of flow of fluids along narrow passages is inversely proportional to the viscosity and that the rate of flow of fluids along narrow capillary passages is proportional to the fourth power of the radius of the capillary. Trevan<sup>2</sup> found that mathematical relations exist between the number of the blood corpuscles and the viscosity. There is a rapidly progressive increase in viscosity as the higher elevations in corpuscular volume are reached. For example, an increase of the percentage of corpuscles by volume of from approximately 50 to 70 doubles the viscosity of the blood. A further increase of from 70 to 82 again doubles the viscosity. These observations probably explain the rather rapid downward course of some of our animals when the higher degrees of concentration were reached.

Underhill and his associates,<sup>3</sup> in a consideration of hemoconcentration with particular reference to burns, stated that an increase of 40 per cent of the normal value is incompatible with life if maintained for an extended period. The condition produced in our experiments was different from that encountered with burns in that the hemoconcentration was not associated with a large diminution in the blood volume. At any rate, a number of animals with an increase in concentration of 50 per cent or more appeared to be in good condition for a number of days.

Peptic ulcers were found in several of the animals. Similar lesions have been reported<sup>4</sup> as occurring in patients with erythrocytosis. A number of explanations for this have been advanced.

Hemoconcentration is usually but not necessarily associated with shock. It is rather generally held that a reduction in the effective circulating blood volume, usually due to a greater loss of plasma than of whole blood, is a constant accompaniment of shock. There is little doubt that marked hemoconcentration plus a reduction in the blood volume exerts more deleterious effects than does an uncomplicated reduction in the blood volume. The present experiments indicate, however, that it is the decline in the blood volume and in the blood pressure with the resulting insufficient supply of oxygen to the tissues that is responsible for the greater part of the alterations that occur in shock.

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2. Trevan, J. W.: The Viscosity of Blood, *Biochem. J.* **12**:60, 1918.

3. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. P.: Blood Concentration Changes in Extensive Superficial Burns, and Their Significance for Systemic Treatment, *Arch. Int. Med.* **32**:31 (July) 1923.

4. Wilbur, D. L., and Ochsner, H. C.: The Association of Polycythemia Vera and Peptic Ulcer, *Proc. Staff Meet., Mayo Clin.* **10**:166, 1935.

## SUMMARY

Marked degrees of hemoconcentration unaccompanied with significant alterations in the blood volume have been produced experimentally by the removal of whole blood and the reintroduction of the red blood corpuscles together with additional ones from compatible donors. Rather marked hemoconcentration produced in this manner is compatible with life in experiments of the duration recorded and does not usually result in significant alterations in the tissues except for vascular engorgement. Whereas both hemoconcentration and reduced blood volume exert deleterious effects in the presence of shock, it is concluded that it is the decrease in the blood volume with the resulting anoxia that is responsible for most of the damage to the tissues. It should be emphasized that these experiments are concerned not with chronic erythrocytosis but with temporary elevations in concentration, such as may occur in association with shock.

## RESULTS OF REMOVAL OF ACOUSTIC TUMORS BY THE UNILATERAL APPROACH

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If any neurologic surgeon were asked to name the most difficult tumor to extirpate, his answer would doubtless be "the acoustic tumor." Until recent years the surgical removal of this type of growth appeared to be almost impossible. In 1917 no less an authority than Cushing<sup>1</sup> wrote: "I doubt very much, unless some more perfected method is devised, whether one of these tumors can with safety be totally enucleated." He was content with removal of the interior of the tumor, by which life could be prolonged, although recurrence was inevitable. Nor could there be any question of the wisdom of his course, for the mortality following total removal at that time was nearly 100 per cent. Successful complete removals of tumors of this type by all of the world's brain surgeons at that time could be counted on the fingers of one hand.

It seemed incredible that a perfectly benign, encapsulated, not too firmly fixed tumor that was potentially curable should present an insoluble problem. The solution came from a realization of the underlying causes of failure and their avoidance. The one important cause of death was injury to the brain stem. And it was then learned that by painstaking dissection of the capsule of the tumor after the interior had been scooped out by successive applications of a curet, trauma to the brain stem could be reduced to a degree compatible with preservation of life and function.

In 1925 I reported<sup>2</sup> a series of 5 cases in which total extirpation was performed in this way without mortality, and in 1934 an important technical advance was added by which the tumor was removed through a small unilateral opening instead of the large bilateral cerebellar exposure. Paradoxically, this restricted cranial opening provided no less operative room and a much easier and better exposure of the tumor; it greatly conserved the patient's resources, and it made the operation far less fatiguing to the surgeon.

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Read at the Sixty-Sixth Annual Meeting of the American Neurological Association, Rye, N. Y., June 8, 1940.

1. Cushing, H.: *Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontile Angle*, Philadelphia, W. B. Saunders Company, 1917.

2. Dandy, W. E.: *An Operation for the Total Removal of Cerebellopontile (Acoustic) Tumors*, Surg., Gynec. & Obst. **41**:129, 1925.



The operative approach with the unilateral exposure is practically identical with that used for trigeminal neuralgia, glossopharyngeal neuralgia and Ménière's disease. To overcome the effects of pressure within the posterior fossa, three space-reducing methods are utilized: (1) tapping the lateral ventricle, which with an average-sized or larger tumor is always dilated; (2) evacuation of the cisterna magna, and

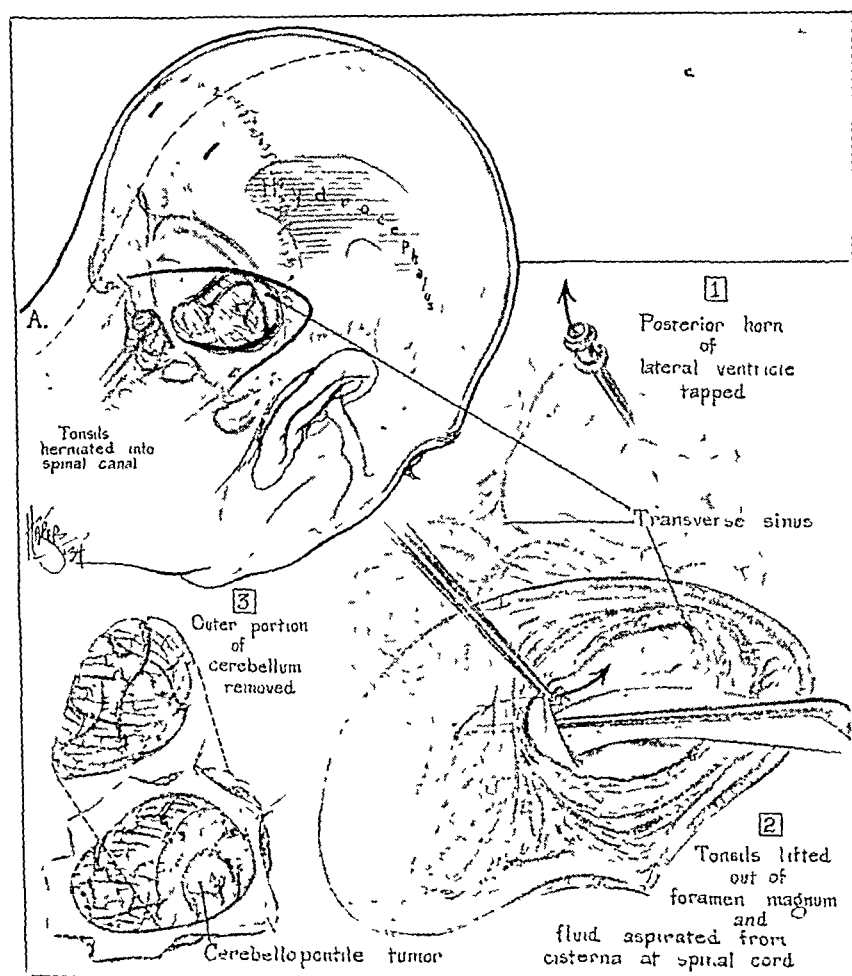


Fig. 1.—A, exposure used in the removal of cerebellopontile tumor by the unilateral approach; 1, method of releasing the supratentorial pressure by puncture of the posterior horn of the lateral ventricle; 2, further release of pressure in the posterior cranial fossa by evacuation of the cisterna magna in the spinal canal, and 3, final stage of exposure by the resection of the outer cap of the cerebellum.

(3) removal of the outer cap of the cerebellar lobe (10 to 15 Gm.). Removal of the cap of the cerebellum results in no appreciable disturbance of function, and by it the exposure of the tumor in the angle is tremendously improved. At times it is not necessary.

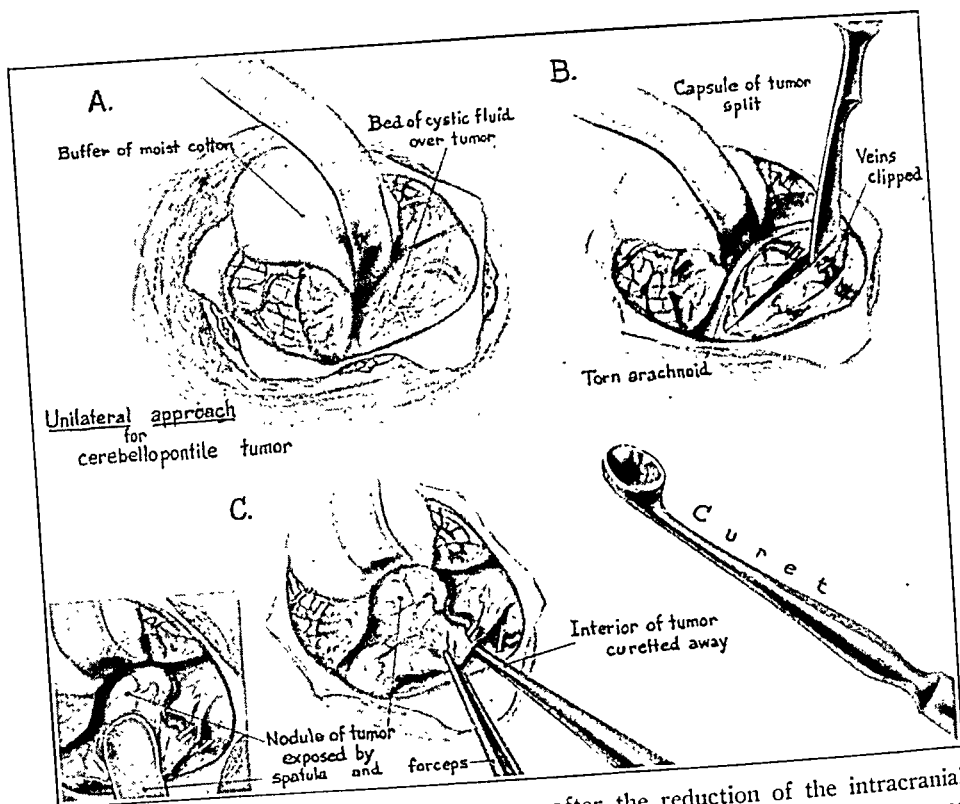


Fig. 2.—Method of attacking the tumor after the reduction of the intracranial pressure: *A*, exposure of the tumor; *B*, splitting of the capsule of the tumor preparatory to intracapsular enucleation, and *C*, gradual withdrawal of the capsule from its bed. The cautery is now used to coagulate all vessels, the silver clips being removed.

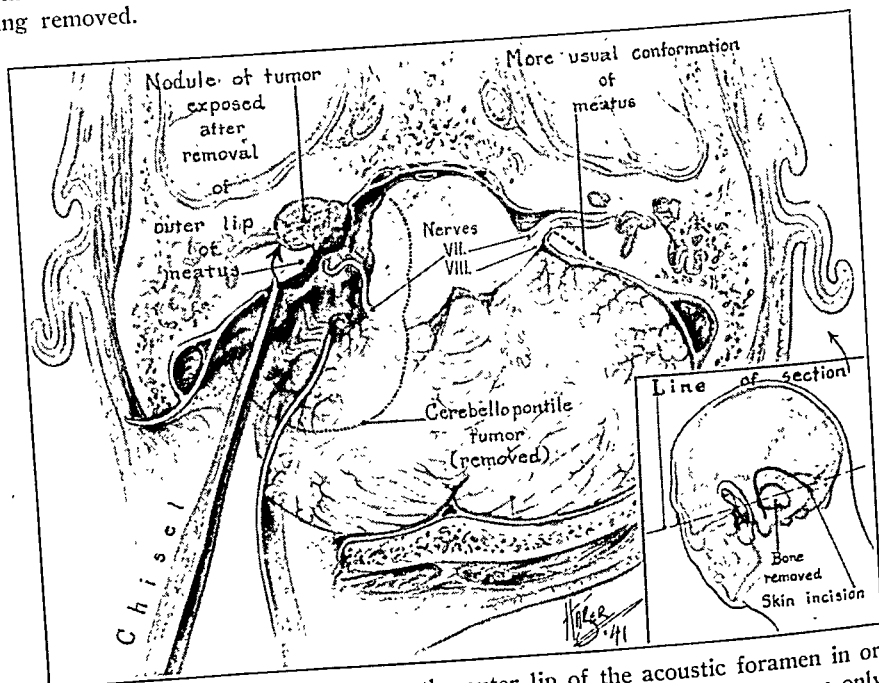


Fig. 3.—Method of cutting away the outer lip of the acoustic foramen in order to remove the tumor extending into the petrous bone. This is necessary only at times.

Most neurologic surgeons, I believe, still cling to partial removal of this tumor, feeling that the mortality associated with total removal is excessive. For reasons that I have stated before, I am convinced that in safe hands total removal is attended by less mortality than is partial removal. The two principal reasons for this statement are: 1. The raw surface of the partially removed tumor becomes very edematous, and this edema extends into the brain stem, causing death. 2. Unless the interior of the upper pole of the tumor is thoroughly removed, the hydrocephalus will not be relieved, and the resultant continued pressure on the brain stem will cause death. By removal of the entire tumor both of these sequelae are automatically avoided, and in nearly every case a patient from whom the tumor has been totally removed has a smooth and uneventful postoperative course.

#### MORTALITY

Since the introduction of the unilateral approach in 1934<sup>3</sup> and with inclusion of the 4 cases with 1 death reported in my paper published at that time, 46 tumors of this type have been operated on and totally removed, with 5 deaths, a mortality rate of 10.87 per cent. The only other known statistics on total removals of such tumors were recently presented by Horrax and Poppen<sup>4</sup> and by Olivecrona,<sup>5</sup> of Sweden. Horrax and Poppen reported a mortality of 10.5 per cent in 19 cases—a rate essentially similar to mine. They used the same unilateral approach. Olivecrona had 14 deaths in 75 total extirpations (mortality rate of 18.7 per cent) during a period of nine years (1930 to 1939). However, with increasing experience his death rate steadily decreased, and from an initial mortality of 26.3 per cent in the first 19 cases it dropped to 11.1 per cent in the last 19 cases. It is interesting that his mortality for total extirpations (18.7 per cent) was less than for subtotal removals (22.2 per cent) or for intracapsular enucleations (28.6 per cent).

In my series,<sup>2</sup> the 5 patients who died were comatose at the time of operation; another had the largest tumor in the series; it weighed 60.5 Gm. In an earlier publication it was emphasized that it appeared to be almost impossible to save a life when an acoustic tumor had induced coma, because the brain stem had already been severely damaged. However, since 1 patient in this series was rescued from coma, the effort should be made to give each patient his only chance by removing the

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3. Dandy, W. E.: Removal of Cerebellopontile (Acoustic) Tumors Through a Unilateral Approach, *Arch. Surg.* **29**:357 (Sept.) 1934.

4. Horrax, G., and Poppen, J. L.: Experiences with the Total and Intracapsular Extirpation of Acoustic Neuromata, *Ann. Surg.* **110**:513, 1939.

5. Olivecrona, H.: Acoustic Tumors, in III<sup>e</sup> Congrès neurologique international. *Comptes rendus des Séances*, Copenhagen, Einar Munksgaard, 1939, p. 701.

growth. It is quite certain that this patient could not have withstood the more extensive bilateral cerebellar approach. One patient was lost when the basilar artery was punctured during an attempt to dissect a remaining tightly bound fragment from it. Although the bleeding was controlled by clipping the basilar artery on each side of the opening in the vessel, the patient died five hours later. One patient died as the direct result of the operation, i. e., injury to the brain stem. The remaining patient died of pneumonia six days after the operation. It should be emphasized in this connection that the patient should not be allowed to swallow until he is fully conscious and then only if there is no impediment in deglutition. Although the vagus nerve is protected as fully as possible during the operation, there may be enough trauma to affect swallowing and cause aspiration into the lungs and pneumonia.

There has been no death in the last 16 cases.

#### LATE RESULTS

Two patients of this series subsequently died, 1 ten months after the operation, from an unknown cause. The other died one year after the operation, from meningitis; a leak of spinal fluid from the ear had followed extensive erosion of the temporal bone by the tumor and had persisted throughout this time. He had survived two attacks of meningitis, one due to *Staphylococcus aureus* and cured by cisternal drainage, and the other due to *Streptococcus haemolyticus* and magically cured almost overnight by sulfanilamide. In the third attack (due to a pneumococcic infection) he died. I had twice tried to find and close the fistulous opening in the temporal bone, but without success. The actual fistula could not be identified.

So far as I know all the remaining patients are living and well. All but a few are active, and many are carrying on their former work in full capacity. Perhaps half a dozen show some degree of uncertainty in walking and have slight ataxia.

Paralysis of the facial nerve must usually be accepted as a necessary sequel of the operation. Except in 2 cases in which the tumor was small, it has been necessary to sacrifice the nerve. Preservation of this nerve would be a most welcome addition to the operation, but its greatly attenuated size and its long course around the posterior wall of the tumor make this exceedingly difficult, for the present at least. Olivecrona has just reported preservation of the facial nerve in 65 per cent of his patients operated on during the past two years.

The loss of function of the facial nerve and the trauma to the trigeminal sensory root—now usually slight—which is so apt to induce neurotrophic disturbances to the eye make it advisable in a high percentage of cases to close the eyelids on that side soon after the operation. Not only will this help to prevent keratitis, but it is the best

treatment after keratitis develops. In none of the cases in this series has the eyeball or the sight been lost. The eyelids are opened when facial function returns, in eight to ten weeks after the customary spino-facial anastomosis performed ten days to two weeks after the removal of the tumor.

In this series injury to the vagus nerve, causing difficulty in swallowing, has occurred rarely and then only for a few days. The vagus nerve

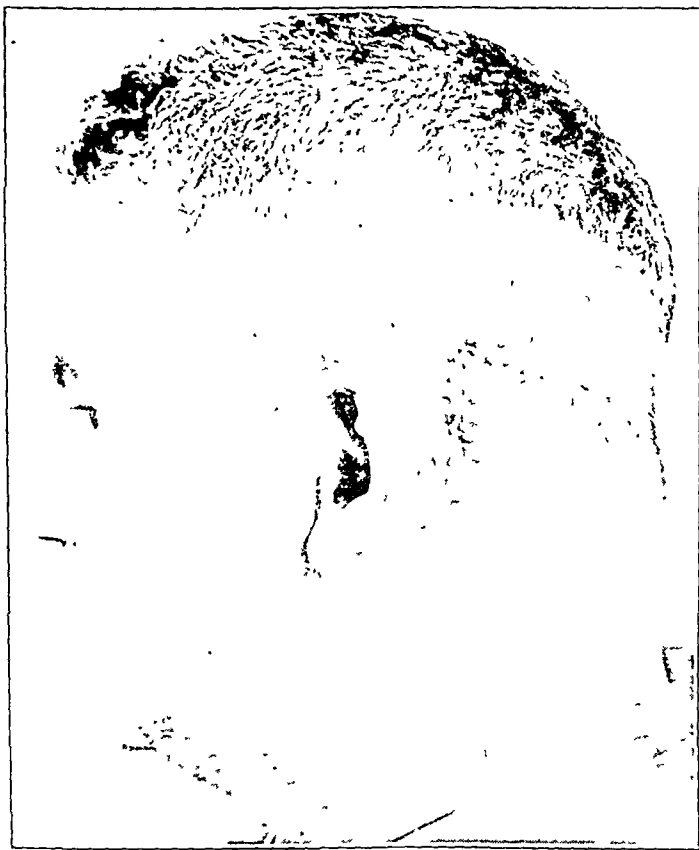


Fig. 4.—Operative wound left by extirpation of the tumor.

is exposed early in the operation and is protected during the remainder of the procedure by a closely applied pledget of cotton.

The eighth nerve is, of course, always lost. Only occasionally is the stump of it seen, and always it diffuses into the tumor. It is interesting that in 34 of the cases in this series there was still good hearing on the surgically treated side before the operation, and in 7 there were remnants of hearing. In 23 the hearing was totally lost. It is possible that by partial removal of only the interior of the tumor the hearing in the 4 cases of good hearing might have been preserved for a time, but

this would appear doubtful, and it is difficult to believe that it could be for long; in any event, it would be poor compensation for the eventual recurrence of the tumor.

In this connection it should be reemphasized that removal of a tumor which has recurred after partial removal carries an excessive mortality because of the dense adhesions between the growth and the surrounding structures. I have had 4 cases of recurrent tumor, with 2 deaths. These have not been included in this series because it is manifestly unfair to the operator to include them—a conviction shared by Horrax and Poppen, who also have excluded cases of recurrent tumor in formulating their excellent results. If these were included the mortality in my series would be 14 per cent. The patient with a recurrent tumor should be given the opportunity of total removal if he wishes it, but he should know that the risk is much increased.

#### SIZE OF TUMOR

In 46 of the cases in this series the weight of the tumor has been recorded. The weights are not strictly accurate, because by the method of continuous suction now employed many pieces of tumor pass down the suction tube and are therefore not included in the total weight. This statement applies principally to the medium and large tumors. Then, too, not infrequently a considerable part, sometimes the major part, of the tumor is cystic, and the weight of the contents is lost. Fourteen tumors weighed less than 10 Gm.; 11 weighed between 10 and 20 Gm.; 11 weighed between 20 and 30 Gm.; 5 weighed between 30 and 40 Gm.; 3 weighed between 40 and 50 Gm., and 2 weighed 66 and 66.5 Gm. respectively; 1 of the latter was saved. The 2 very large tumors were probably near the extreme limit for this type. A tumor weighing between 30 and 40 Gm. would doubtless cause death in most cases before its size had increased much more. It is hardly necessary to add that the size of the tumor is a very important index of the risk assumed in the operation. It is encouraging that 25 of the 40 tumors weighed under 20 Gm. In none of the cases in which the growth was of this size did death occur. Several of the smaller tumors were encountered during operation for trigeminal neuralgia by the cerebellar route. A tumor is at times suspected in a patient with tic douloureux because of some reduction in hearing on the affected side, but frequently the tumor is found entirely unexpectedly, there being no difference in the character of the neuralgia when a tumor is the underlying cause. In approximately 10 per cent of cases trigeminal neuralgia is caused by a tumor in the cerebellopontile angle, and in a fair share the tumor is an acoustic neuroma.

## AGE; SEX; SITE OF TUMOR

The highest incidence of the acoustic neuroma is in the fourth decade. Sixteen, or nearly one third, of the patients were between 40 and 50; 11 were between 30 and 40, 7 between 20 and 30, 7 between 50 and 60 and 4 between 60 and 70. The youngest patient was 18 years old; this was the only one under 20. There was a higher incidence in women, the ratio being 28 women to 18 men. There is essentially no difference in the topographic incidence; 25 of the tumors occurred on the right side and 21 on the left.

## RECURRENCE

There has been no recurrence in any case in this series, nor do I know of any recurrence of a growth of this type since the inception of the operation for total removal eighteen years ago. Since the tumor practically always projects some distance into the acoustic foramen, it *seems essential that this extension of the growth be totally extirpated if* recurrence is to be avoided. I have consistently extirpated it. Frequently it is necessary to chisel away the outer lip of the acoustic foramen in order to gain access to this hidden retreat of the final fragments of the tumor.

# VISUALIZATION OF THE PULMONARY ARTERY DURING ITS EMBOLIC OBSTRUCTION

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AND

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The purpose of this study was to work out a simple method of visualizing the pulmonary artery in the dog as Robb and Steinberg have done in man<sup>1</sup> and then to study the vascular bed after the administration of drugs and after the production of embolism. In a previous publication<sup>2</sup> the effect of embolism on the coronary circulation has been reported. In this paper we wish to report our observations on the effect of pulmonary embolism on the pulmonary vascular bed of the dog. Two hundred and sixty-three films were obtained of 48 dogs. The pulmonary vascular tree was first studied by injection of a barium sulfate suspension into the pulmonary conus distal to its ligature. Various angles were employed, and finally the right anterior and left anterior oblique positions were selected (fig. 1). The anteroposterior view shows that only the left pulmonary artery is filled adequately. In the oblique views, attention should be called to the superior pulmonary artery, the changes in whose caliber have been watched with special care. The left anterior oblique position prevented the heart shadow from overlapping the pulmonary arterial tree, and, unless otherwise stated, this position was used in all experiments on the living dog.

The amount and concentration of the opaque solution had to be determined next. Several colloidal solutions of iodine, such as hippuran, diodrast and neo-iopax, were employed. Finally a 25 per cent solution of sodium iodide was selected, which was well tolerated in 15 to

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From the Department of Surgery, University of Illinois College of Medicine.

1. Robb, G. P., and Steinberg, I.: Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Vessels in Man, *Am. J. Roentgenol.* **41**:1, 1939; Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Vessels in Heart Disease, *ibid.* **42**:14, 1939; Visualization of the Chambers of the Heart and Thoracic Blood Vessels in Pulmonary Heart Disease: A Case Study, *Ann. Int. Med.* **13**:12, 1939.

2. de Takáts, G.; Beck, W. C., and Fenn, G. K.: Pulmonary Embolism, *Surgery* **6**:339, 1939. de Takáts, G., and Jesser, J. H.: Pulmonary Embolism, *J. A. M. A.* **114**:1415 (April 13) 1940.



20 cc. doses. A 13 gage needle was used, the solution being injected in less than one second and the exposures made at three and five seconds respectively after the completion of the injection. In figure 2 are shown a control film (a) and two exposures (b) and (c) made at three

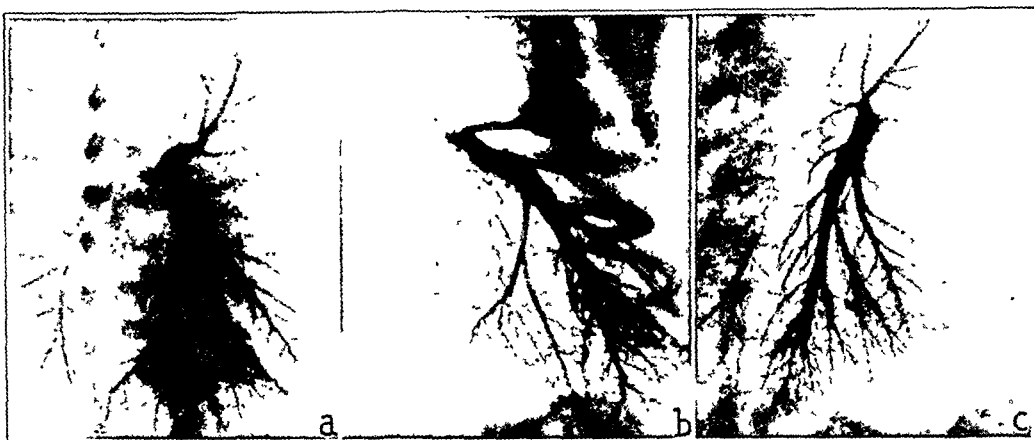


Fig. 1.—The anteroposterior view (a) shows that only the left pulmonary artery has been filled adequately. The left anterior oblique view (b) shows that the heart shadow has been eliminated from overlapping the vascular tree. The right anterior oblique view (c) does not show the same spread of branches as the preceding one. Unless otherwise specified, the left anterior oblique view has been employed in all of the following films. These injections were made on dead dogs with the thorax open; barium sulfate was used for the opaque substance.



Fig. 2.—An oblique view of the heart (a) prior to injection; (b) three seconds after injection of 20 cc. of 25 per cent sodium iodide solution (the superior vena cava, the right side of the heart and the left and right pulmonary arteries are visualized; the left side of the heart and the inferior vena cava are not filled), and (c) five seconds after injection. The iodine solution has left most of the arterial branches and is in the veins. The left side of the heart is visualized, as is the inferior vena cava passing through the diaphragm.

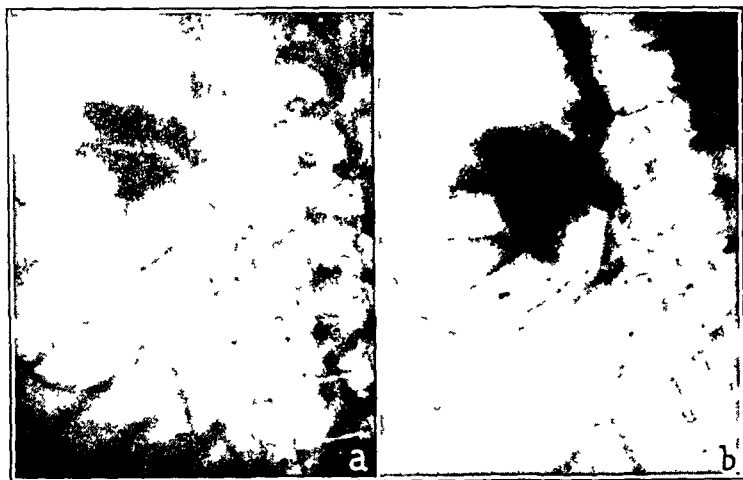


Fig. 3.—Exposure after three seconds (*a*) before the administration of papaverine; exposure of the same animal (*b*) treated by injection the second time, five minutes after the intravenous injection of 2 grains (0.12 Gm.) of papaverine. Note the widening of the superior vena cava, the enlargement of the right side of the heart and of the pulmonary conus. The diameter of two arterial branches running toward the spine and the diaphragm is definitely larger after administration of papaverine.



Fig. 4.—Exposure after three seconds before the administration of epinephrine (*a*) and exposure of the same animal in an identical position (*b*) two minutes after the intravenous injection of 1 cc. of a 1:1,000 solution of epinephrine hydrochloride. Note the marked contraction of the right auricle, the potent reflux of the opaque solution in both venae cavae and the enlargement of the pulmonary conus. The superior vena cava is tortuous and spastic; branches of the pulmonary artery, especially in the upper lobe, have a diminished vascularity. The whole picture is that of an increased resistance in the pulmonary vascular bed.



Fig. 5.—After a control visualization (a) a massive pulmonary embolism has been produced with 2 cc. of an iron chloride-barium sulfate mixture. Note (b) the marked enlargement of the right side of the heart, the reflux in both venae cavae, with bulbous dilatations at their entrance to the heart, and the complete obstruction of the left pulmonary artery. The right pulmonary artery is invisible. In c the obstruction is more peripheral in the left pulmonary artery, with a mural defect (parietal thrombus) proximal to the obstruction. Again the right pulmonary artery is invisible. In this film the bulbous dilatation of the two venae cavae is even more pronounced.

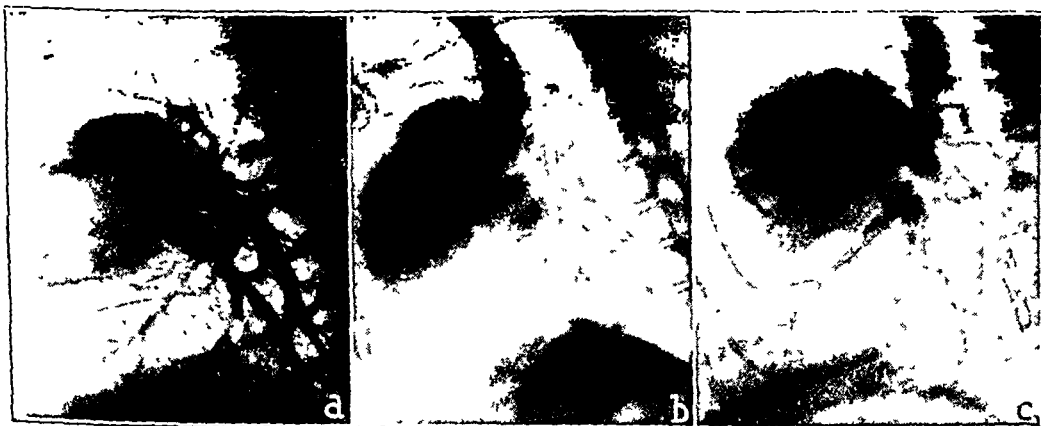


Fig. 6.—A control visualization (a) was made of the pulmonary arterial bed. A pulmonary arterial embolism was produced with 1.5 cc. of the embolizing substance (b). Note the shift of the longitudinal axis of the right side of the heart, the cor pulmonale, the block in the left pulmonary artery and the tapering of the smaller vessels of the lower lobe of the right lung. The upper lobes are vascular. An embolism was produced (c) with 1 cc. of the embolizing substance. A peripheral embolus is seen close to the spine. It has been retouched to demonstrate it in the reproductions. There is no cor pulmonale.

and five seconds respectively after the injection of the solution. In the film taken at three seconds one can recognize the superior vena cava, the right auricle and ventricle and the left and the right pulmonary arteries with their branches. The inferior vena cava, the left side of the heart and the aorta are not visualized. In the film taken at five seconds most of the opaque material is seen in the left ventricle; the aorta and the inferior vena cava can be well seen. The solution has disappeared from the superior vena cava; some of it is still in the pulmonary vascular bed.

Figure 3 illustrates the effect of 2 grains (0.12 Gm.) of papaverine hydrochloride on the visualized pulmonary artery. Exposures were made in the left anterior oblique position at three seconds. Note the widening of the superior vena cava, the enlargement of the pulmonary

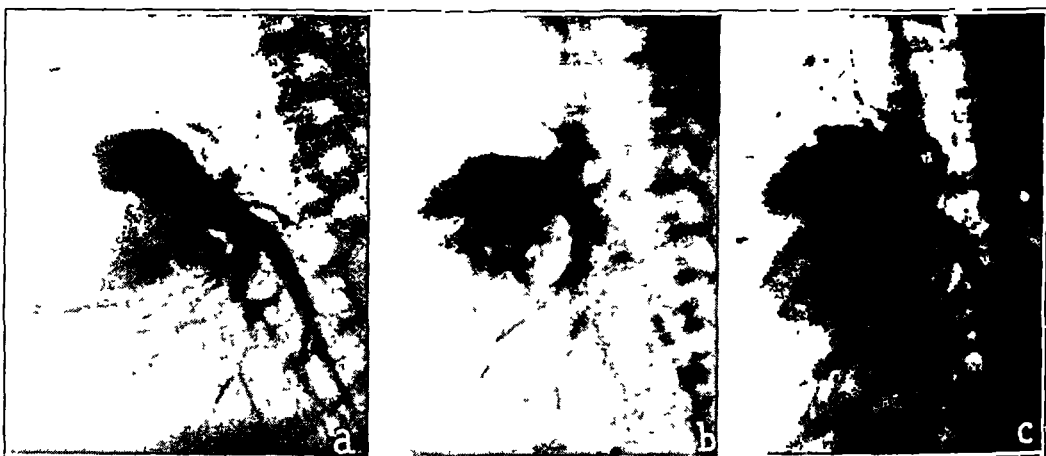


Fig. 7.—In the control film (a), note the superior pulmonary artery and three branches of the right pulmonary artery. These are obstructed in the next film (b), which shows a peripheral type of pulmonary embolism produced with 0.5 cc. of the embolizing substance. There is no cor pulmonale. Filling defects are seen in three branches of the right pulmonary artery, just above the diaphragm. Note the avascular and emphysematous upper lobe. The same animal was revisualized (c) after intravenous injection of 1 grain (0.06 Gm.) of papaverine hydrochloride. Note the marked change in the vascularity of the upper and the lower lobe. There is more vascularity than in the control film.

conus and the increase in diameter of some of the branches. The inferior vena cava is devoid of the opaque solution.

In contrast to this, the effect of epinephrine hydrochloride, 1 cc. of 1:1,000 solution given intravenously, is shown in the next film (fig. 4). There was a potent reflux of the opaque solution into the pulmonary conus and into the superior and the inferior vena cava, indicating an increased resistance and pressure in the pulmonary vascular bed. This film gives roentgen evidence of the rise in pulmonary arterial pressure following the use of epinephrine.

In the following series (fig. 5), after a visualization at three seconds (*a*) a massive pulmonary embolism was produced with 2 cc. of modified Martin solution as used in our previous experiments. This solution consists of equal parts of barium sulfate and physiologic solution of sodium chloride. In several hundred experiments from our laboratory the size and site of the embolus were fairly well controlled by the dose. The block in the second film (*b*) is close to the right side of the heart; the right ventricle and the origins of the two venae cavae are distended. The pulmonary conus is hardly visible. In the next film (*c*) the block of the pulmonary artery is at a lower level. Note in both films, however, the marked *cor pulmonale* and the bulbous enlargements of the superior and the inferior vena cava.

In the next series (fig. 6), after the control visualization (*a*) an embolus was produced with 1.5 cc. of the Martin solution. Note again (*b*) the distention of the right side of the heart, its twisting into the longitudinal axis and the marked back pressure into the superior and the inferior vena cava. The pulmonary arterial tree is greatly reduced in size; there is a block of the left main branch, and there is marked tapering of two branches in the lower lobe of the right lung. In the third film (*c*) peripheral obstruction is shown, but there is no *cor pulmonale*.

In the last series (fig. 7) the effect of 0.5 cc. of Martin's solution on the pulmonary vascular bed and the effect of papaverine are demonstrated. Note the filling defects in three branches of the right pulmonary artery. Note the change in vascularity and the disappearance of emphysema after the administration of papaverine.

#### COMMENT

This, of course, is a rather crude method of studying the effect of pulmonary embolism on the right side of the heart and the pulmonary artery; it has, however, the advantage of allowing study of the intact living animal, whose reactions have not been disturbed by cannulas or operative procedures in the thorax and whose lung and heart have not been isolated and perfused. For the interpretation of these films, however, direct measurements of pressures are necessary.<sup>3</sup> The sudden dilation of the right side of the heart and of the vena cava following obstruction to the pulmonary artery could be readily demonstrated. Interesting is the shift of the long axis of the right side of the heart in some of the films. Attention should be drawn to the marked pressor effect of epinephrine in the pulmonary vascular bed, which was shown

3. Katz, L. N., and Steenitz, F. S.: Pulmonary Arterial Pressure in Renal Hypertension, *Am. J. Physiol.* **128**:433, 1940.

by Katz some years ago.<sup>4</sup> The use of this drug, as we have pointed out elsewhere, is to be condemned in cases of pulmonary embolism. Even comparatively small doses given when the pulmonary arterial pressure is already abnormally high may lead to pulmonary edema.<sup>2</sup> Papaverine, on the other hand, seems to have a relaxing effect on the smooth muscle of the pulmonary vascular bed. It also has a bronchodilator effect, on which we shall report later. Other drugs now clinically used for pulmonary embolism can be studied by this method.

In the presence of total block of the pulmonary artery the death of the animal cannot be prevented. In the presence of partial occlusion, which occurs frequently in man, medication to eliminate the reflex effects of distention of the vascular tree proximal to the obstruction has saved the animal in 50 per cent of the experiments. Thus, atropine sulfate abolishes reflexes from the right side of the heart and the great veins and also from the numerous pressor receptors situated at the obliterated ductus botalli. They have been demonstrated in man histologically<sup>5</sup> and have been shown, by Schwiegl,<sup>6</sup> to have depressor effects. In addition, we believe that we have demonstrated increased vascularity following the use of papaverine, a hitherto unsettled question. Whether this means a relaxation of the smooth muscle of the arteries or is due to a rise in pulmonary arterial pressure could be settled only by direct measurements of pressure in the pulmonary artery. We feel that the results of emergency treatment of pulmonary embolism as proposed from our clinic, consisting of administration of oxygen and intravenous injection of atropine and papaverine, seem to indicate that the use of papaverine should be continued.

Our observations also support the idea, especially promulgated by Daly and his co-workers, that the pulmonary vascular bed is richly supplied with sensory receptors and that the pulmonary vascular system possesses a potent vasoconstrictor mechanism which is under control of the sympathetic nervous system.<sup>7</sup> Drugs which increase blood flow to the pulmonary arterial bed by increasing the output of the right side of the heart, such as epinephrine, neo-synephrin and digitalis, may do harm in cases of pulmonary embolism, as they increase the pulmonary hyper-

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4. Johnson, V.; Hamilton, W. F.; Katz, L. N., and Weinstein, W.: Study on the Dynamics of the Pulmonary Circulation, *Am. J. Physiol.* **120**:624, 1937.

5. Unpublished data.

6. Schwiegl, H.: Der Lungenentlastungsreflex, *Arch. f. d. ges. Physiol.* **236**:206, 1935.

7. de Burgh Daly, I.; Ludany, G.; Todd, A., and Verney, F. B.: Sensory Receptors in Pulmonary Vascular Bed, *Quart. J. Exper. Physiol.* **27**:123, 1937. de Burgh Daly, I.; Foggie, P., and Hebb, C. O.: An Experimental Analysis of the Action of Adrenaline and Histamine on Different Parts of the Pulmonary Vascular Bed, *ibid.* **30**:21, 1940.

tension and accelerate the impending failure of the right side of the heart. Digitalis, in addition, sensitizes the vagus nerve and facilitates the operation of vagal reflexes on the coronary vessels, bronchi and gastrointestinal tract." Its use in cases of pulmonary embolism is to be condemned.

#### SUMMARY

Of a total of 48 dogs, two hundred and sixty-three films were taken with the object of visualizing the pulmonary arterial tree under basic conditions and under the influence of epinephrine and papaverine. The pulmonary arterial hypertension and its effects on the circulation are discussed. There seems to be some added evidence for the assumption that relaxation of the vascular bed may contribute to the recovery of patients suffering from pulmonary embolism.

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# TRAUMATIC VASOSPASTIC DYSTROPHY OF THE EXTREMITIES

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After almost any form of injury to an extremity or to its nerve or blood supply a peculiar type of syndrome may ensue which has been variously designated, depending on the chief clinical manifestations, for instance as Sudeck's atrophy,<sup>1</sup> painful osteoporosis,<sup>2</sup> traumatic vasospasm<sup>3</sup> and reflex dystrophy.<sup>4</sup> (Causalgia<sup>5</sup> probably belongs to this group. However, marked dilatation rather than spasm seems to be the predominant vasomotor disturbance associated with that condition.) The initial injury may be trivial, such as straining of a ligament or pricking of a finger; or it may be more serious, such as a fracture, a dislocation or a gunshot wound. The syndrome may regress spontaneously, or it may go on to advanced disturbances involving skin, connective tissue, nerves, muscles, joints and bone. Pain, subjective coldness, objective coldness, hyperhidrosis, cyanosis, tense, shiny skin, firm, tender edema, muscular weakness, joint fixation and decalcification of bone have all been observed. The hands and the feet are primarily involved.

De Takáts<sup>4</sup> stressed the reflex origin of the vasomotor disturbance. He postulated a continuous flow of afferent stimuli from the injured tissue which reach the spinal cord, where they reflexly activate cell stations of the sympathetic nervous system, with resultant production of efferent vasomotor and sudomotor impulses. Treatment consists of breaking the reflex arc. On the afferent side this may be accomplished by healing the initial and irritating injury. However, the dystrophy, when once established, may persist despite apparent healing of the

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From the Peripheral Vascular Service, Department of Orthopedics, Mount Sinai Hospital.

1. Sudeck, P.: Ueber die akute entzündliche Knochenatrophie, *Arch. f. klin. Chir.* **62**:147, 1900.

2. Fontaine, R., and Hermann, L.: Posttraumatic Osteoporosis, *Ann. Surg.* **97**:26, 1933.

3. Lehman, E. P.: Traumatic Vasospasm, *Arch. Surg.* **29**:92 (July) 1934.

4. de Takáts, G.: Reflex Dystrophy of Extremities, *Arch. Surg.* **34**:939 (May) 1937.

5. Mitchell, S. W.; Morehouse, G. R., and Keen, W. W.: Gunshot Wounds and Other Injuries of Nerves, Philadelphia, J. B. Lippincott & Co., 1864.



original lesion; a vicious circle may be established by which the vasomotor disturbance prevents the healing of the traumatic lesion, or the lesion may be such as to render direct surgical attack impractical or inadvisable. For these reasons it is often necessary to interrupt the reflex arc on its efferent side by means of a sympathectomy.

#### REPORT OF CASES

CASE 1.—W. McG., a 27 year old white man, came under my observation in May 1939. Ten months previously he had fallen from a scaffold and had suffered a fracture-dislocation of the right sacroiliac joint and multiple fractures of the transverse processes of the lower lumbar vertebrae. The accident was immediately followed by total paralysis of the right leg and foot and by anesthesia of this foot. Four months later, when he became ambulatory, he began to experience two types of pain. One was lancinating and radiated down the back of the extremity into the heel. The other was a peculiar pain felt in the deep structures of the anesthetic foot. The latter pain was present constantly, was worse at night and required narcotics for relief. It appeared to be definitely aggravated by the intermittent nerve root pain. Since the onset of this pain he had become totally incapacitated and was in danger of becoming addicted to narcotics.

*Examination.*—The arteries throughout the right lower extremity pulsed normally. The foot was fixed in extreme plantar flexion. It was edematous; the skin was tense and shiny and was covered with perspiration. When the foot was exposed in a cool room the surface temperature dropped rapidly, and in the dependent position the foot became intensely cyanotic. The picture was that of a marked vasomotor disturbance consisting of arteriolar constriction with capillary dilatation and stasis. Roentgenographic examination revealed spotty decalcification.

Neurologically there was total paralysis with atrophy of all the musculature distal to the knee. The foot was anesthetic to all forms of stimulation. However, the sympathetic innervation of the foot appeared to be intact, as was evidenced by the hyperhidrosis of the foot and by a marked rise in the surface temperature of all parts of the foot following a paravertebral procaine hydrochloride block of the lumbar portion of the right sympathetic trunk. These findings could be interpreted only on the basis of a division of the fourth and fifth lumbar and first sacral spinal nerves central to the points where the post-ganglionic vasomotor and sudomotor fibers entered these spinal nerves to be distributed to the blood vessels and sweat glands of the anesthetic foot.

*Course.*—After the aforementioned procaine block of the lumbar portion of the sympathetic trunk the foot became hot and dry, the edema subsided and the pain in the foot promptly disappeared. Relief persisted for a few days, at the end of which time the entire syndrome recurred. The procaine block was repeated, with similar results. A diagnosis of intermittent irritation of the central ends of the severed fourth and fifth lumbar and first sacral spinal nerves with a resultant reflex vasomotor disturbance in the foot was made. A lumbar sympathectomy was performed on the right side. The operation gave immediate relief of the pain in the foot and of the vasomotor disturbances. A triple arthrodesis was then performed by Dr. A. Miller. An excellent weight-bearing foot was obtained. The foot has remained warm, dry and of good color, and the patient has returned to work and is completely ambulatory. The attacks of

nerve root pain have persisted. However, they have not proved sufficiently severe to be disabling or to warrant further surgical intervention. The spotty decalcification has disappeared.

Since the initial injury did not involve the foot and since only the sympathetic nerve supply remained intact after the injury, the reflex origin of the vasomotor disturbances and the resultant pain is obvious. It is also evident that, since these sensations of pain could have reached the central nervous system only via sympathetic nerve pathways, the origin of the painful sensations must have been in structures innervated by sympathetic nerve tissue, and these, for practical purposes, could only have been peripheral blood vessels.

The mechanism of production of pain in cases of peripheral vascular disease is not entirely clear. Ischemia per se is unquestionably a potent cause. Intermittent claudication and the pain of impending gangrene undoubtedly originate in the stimulation of extravascular pain fibers by acid metabolic substances. However, the role which blood vessel sensibility itself plays is still debatable, although there is abundant clinical evidence that it exists and that the pain impulses are carried over sympathetic nerve pathways. The difficulty lies in the fact that laboratory investigators have not been able to demonstrate experimentally that the peripheral blood vessels possess sensibility to pain stimuli. Stopford<sup>6</sup> was unable to prove the existence of ascending sensory fibers from the blood vessels. Woollard<sup>7</sup> and Kuntz<sup>8</sup> were unable histologically to demonstrate sensory nerve endings in the intima of arteries or in capillary endothelium.

The most consistent and sustained attempts to demonstrate intrinsic peripheral vascular sensibility have been made by Moore and Singleton. The results of these experiments have been reviewed and summarized in a recent publication by Moore.<sup>9</sup> The experiments of these workers have consisted essentially of the injection of irritating solutions down a peripheral artery, such as the femoral, in a decerebrate or a barbitalized animal, and noting the production of a pseudoaffective reaction. In addition, they manipulated and stimulated the blood vessels in various other ways in an attempt to elicit pseudoaffective reflexes. (A pseudoaffective response is a type of reflex motor expression occurring in a decerebrate animal which could be attributed to painful stimuli reaching the brain. It consists of snapping of the jaws, baring of the teeth,

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6. Stopford, J. S. B.: The Innervation of Blood Vessels in the Limbs, *Lancet* 2:779, 1931.

7. Woollard, H. H.: The Innervation of Blood Vessels, *Heart* 13:319, 1926.

8. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1934.

9. Moore, R. E.: Some Experimental Observations Relating to Visceral Pain, *Surgery* 3:534, 1938.

snarling, movements of the limbs, dilation of the pupils, etc.) Injections of certain types of irritant solutions in proper concentration invariably resulted in strong reflex expressions which could be attributed to pain. These reflexes could not be abolished by severing the arterial trunk proximal to the point of injection or by sympathectomy. They could be abolished, however, by sectioning all the spinal nerves innervating the extremity being tested. Thus, section of all the trunks of the lumbosacral plexus would eliminate reaction to injection of an irritant into the femoral artery. The experimenters found that stimulation resulted only when the irritating solution was allowed to reach the capillary bed where it was able to diffuse into the adjacent tissues. It was there that the actual stimulation of sensory nerve endings with pain production took place. These investigators were unable to elicit pseudo-affective reflexes by forcibly distending an artery or by throwing it into spasm. When an artery was carefully isolated from its accompanying nerve trunks, no form of mechanical manipulation, such as clamping or ligation, would produce a reflex disturbance. From these results they concluded that the walls of the peripheral vessels are insensible to pain-producing stimuli.

There are certain deficiencies in all experiments of this type which limit their usefulness in interpretation of disease states in the human organism. For instance, there is the question of oversimplification. Peripheral vascular disease is a pathologic process, infinitely more complex than the simple expedient of injecting an irritant solution into a normal vascular bed. But there is an even more fundamental criticism to be levied against the basic premise on which the conclusion was based that the peripheral blood vessels are insensible to pain. This premise is the assumption that since pseudoaffective reactions did not attend direct stimulation of the blood vessel wall the animal would not have felt pain had it been possessed of all its faculties. Pseudoaffective responses are by no means a sensitive indicator of pain. The foregoing case illustrates that the mechanism of pain production in the presence of peripheral vascular disease is at times inexplicable unless the presence of intrinsic vascular sensibility to pain-producing stimuli is assumed.

The following case illustrates that the trauma giving rise to the reflex vasomotor disturbance may be of internal origin.

CASE 2.—Mrs. S. A., a 55 year old white woman, was seen in August 1940. She stated that for many years she had been troubled with numbness and tingling in the fingers of her left hand. However, she had not been particularly concerned until recently, when severe aching pain in the wrist and hand had appeared; when the wrist became suddenly stiff and swollen, she became alarmed and sought relief.

*Examination.*—Neurologically the patient presented marked muscular weakness in the distribution of the ulnar nerve in the left hand. She was unable to flex

the fifth finger, and there was conspicuous atrophy of the ulnar side of the forearm. There was also a marked diminution of cutaneous sensibility in the peripheral distribution of the ulnar nerve. These signs and symptoms suggested the presence of a cervical rib; so a roentgenogram was taken of the lower part of the cervical portion of the spine. No cervical ribs were present, but the transverse processes of the last cervical vertebra were enlarged.

In addition to these neurologic findings, there was evidence of a well established vasomotor disturbance. The hand was cold and covered with perspiration. There was firm, painful edema, which appeared to involve the sheaths of the flexor tendons of the wrist. Motion of the wrist joint was impossible because of this edema. Roentgen examination showed marked decalcification of the bones of the hand and of the wrist joint. The upper end of the right thoracic trunk was anesthetized with procaine hydrochloride. Within a few minutes of the injection the pupil constricted and the hand became hot and dry. Within thirty minutes the edema had subsided so that the patient was able to move the wrist joint without pain. Relief persisted for several hours. The block was repeated one week later, with similar transient relief. A diagnosis of scalenus anticus syndrome with reflex vasospastic dystrophy was made, and operation was advised. A Telford sympathectomy<sup>10</sup> through the supraclavicular approach was considered the procedure best suited to the needs of this patient. To expose the sympathetic trunk through the posterior cervical triangle, section of the scalenus anticus muscle is necessary. It would thus be possible to relieve the entire condition with a single operation. Within twenty-four hours after the operation the edema about the wrist joint had subsided; the pain in the hand and wrist joint had disappeared, and active motion of the wrist joint was again possible. The paresis of the ulnar nerve and the anesthesia have also disappeared, but more slowly.

The following case illustrates the more conservative method of handling traumatic vasospastic dystrophy by means of procaine blocks of the reflex sympathetic pathways combined with treatment directed toward healing the exciting lesion.

CASE 3.—I. P. came under observation March 11, 1940. In January she had fallen and had dislocated her right shoulder joint. After reduction the injured shoulder became increasingly painful and stiff. In addition, she began to experience severe pain in the hand; the fingers became swollen, and motion of the fingers was limited by the painful swelling.

*Examination.*—When first seen, the arm was kept pressed to the side of the body, and the painful hand was supported by the other. There was diffuse tenderness about the right shoulder joints, and any motion, either passive or active, was impossible. The hand was cold and covered with perspiration. The fingers were edematous, and the skin was tense and shiny. Motion of the fingers was impossible because of the firm, painful edema. Roentgen examination of the shoulder and of the hand showed spotty decalcification. A diagnosis of a chronic injury to the periarticular structures of the right shoulder joint with reflex vasospastic dystrophy was made. The upper end of the right thoracic sympathetic trunk was blocked with procaine hydrochloride. Within a short time the right hand became warm and dry and the pain disappeared. It was then possible to abduct

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10. Telford, E. D.: The Technique of Sympathectomy, *Brit. J. Surg.* **23**: 448, 1935.

the right arm passively to an angle of 90 degrees without pain. An airplane splint was applied. From that time on improvement was rapid. The splint was worn for several weeks and then discarded. The block was repeated once for some residual pain in the hand. At present the patient is free from symptoms; an adequate range of motion has been restored to the shoulder and hand, and the hand is normal in appearance.

#### COMMENT

I have been impressed with the fact that in all cases of this syndrome which I have personally observed the patients were suffering from a severe anxiety neurosis. The psychologic aspects of the syndrome have been stressed by other observers. The emotional mechanisms involved are not entirely clear. However, it seems that long-continued and unrelieved painful stimulation of sympathetic nerve tissue is in itself capable of producing profound anxiety. If free floating anxiety is already present, the addition of further anxiety resulting from pain referable to the sympathetic nervous system not only may reenforce the former but may serve to focus it on the painful part. A vicious circle may thus be established. For that reason, only therapeutic measures which are likely to relieve the pain should be employed. From a psychologic point of view, treatment which fails is worse than no treatment.

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## X. THE INADEQUATELY TREATED CRETIN

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The inadequately treated child with hypothyroidism may present diagnostic problems related to growth, and because of this a tendency has arisen to ascribe to understature an element of anterior pituitary growth deficiency and to administer anterior pituitary extracts containing the growth-stimulating factor, exclusively or combined with wholly inadequate thyroid therapy.<sup>1</sup> The pallor associated with this condition occasionally leads to a diagnosis of secondary anemia of unknown cause. The constipation, protuberant abdomen and megacolon that may be observed in the inadequately treated cretin may be mistaken for Hirschsprung's disease. We are presenting a case in which these diagnostic difficulties were encountered.

### REPORT OF CASE

In October of 1939 M. B., a white boy aged 15 years, was referred to the hematology department because of anemia. Hematologic studies, including a sternal puncture, revealed an anemia which was not characteristic of any definite disease. This patient was referred to us in January 1940 because of his understature, for which he had received considerable amounts of growth-promoting material prior to his entrance into our institution, without any appreciable results. Our impression from a cursory examination was that of thyroid deficiency (fig. 1). We were especially interested in learning that a lumbar sympathectomy had been performed for Hirschsprung's disease.

M. B. was the fourth child. He was born at full term, weighing 10 pounds (4,535 Gm.). His condition at birth was apparently good. He presented a difficult feeding problem. The developmental processes were definitely retarded. He was slow in holding his head erect, sitting and crawling; he walked at 30 months and began talking at 32 months. Eczema was present in infancy, and he contracted pertussis, with an apparently uncomplicated, uneventful recovery. His father (70½ inches [178 cm.] tall) is living and well, as is also the mother (63 inches [160 cm.] tall), who underwent a thyroidectomy twenty years ago. There are 4 siblings living and well; 3 are older and 1 younger than our patient. There is no other history of endocrine disturbance in the family.

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From the Department of Pediatrics (Endocrine Clinic), University of Illinois College of Medicine, and the Research and Educational Hospital.

1. Rowntree, L. G.: Thyroid Therapy in Juvenile Myxedema, *J. Pediat.* **16**: 770 (June) 1940.

At about  $2\frac{1}{2}$  years of age, because of slow growth, constipation, a large abdomen and an umbilical hernia, M. B. was taken to a physician, who made a diagnosis of cretinism. From this period to the age of 13 years he received thyroid,  $\frac{1}{2}$  grain (0.03 Gm.) daily. The parents report that during this time his growth was very slow; the pallor persisted; the abdomen became progressively larger, and constipation persisted, with large, hard stools every two or three days.

In March 1938 the parents sought further medical attention. At this time the child's condition was diagnosed as Hirschsprung's disease, for which the presacral nerve and the last three lumbar sympathetic ganglions with the intervening

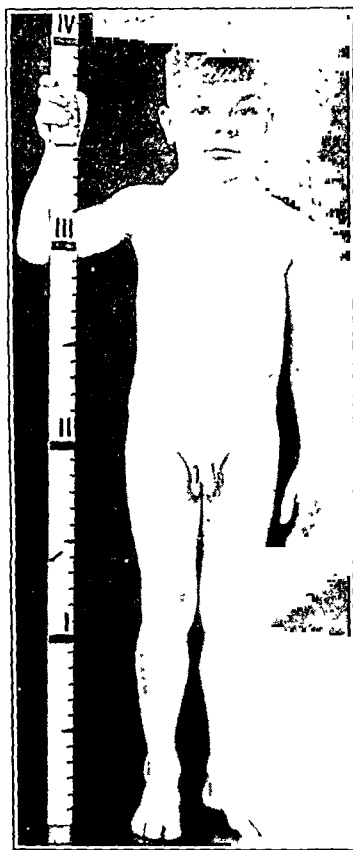


Fig. 1.—Photograph of M. B. taken in February 1940, at the age of 15 years.

trunk were removed. After this operation the thyroid therapy was discontinued and he was treated with an anterior pituitary extract containing the growth-promoting factor for a period exceeding a year, without any response in growth. He also received large doses of stomach U. S. P. (ventriculin) and iron, which resulted in no change in his anemia.

In January 1940, when he first saw M. B., examination revealed him to be phlegmatic and dwarfed. He weighed 61 pounds (27.7 Kg.) and measured  $48\frac{3}{4}$  inches (124 cm.), which is  $40\frac{1}{2}$  pounds (18 Kg.) and  $13\frac{3}{4}$  inches (35 cm.) below normal for his age. His span was  $48\frac{3}{8}$  inches (123 cm.); the upper measurement (pubis to vertex), was  $25\frac{1}{8}$  inches (63 cm.), and the lower (pubis to sole),

23½ inches (59 cm.). The bi-iliac measurement was 8½ inches (21 cm.). Marked pallor was present. The skin was dry, and the scalp hair was coarse. The pupils reacted to light and in accommodation. The ocular fundi and the visual fields were normal. He had twenty-three teeth, which were mottled; a number had cavities, and some were deciduous. The neck was short, and the thyroid area was bare, giving the examiner the sensation of palpating a naked trachea. Supra-clavicular fat pads were present. The heart and lungs were apparently normal. The systolic blood pressure was 100 mm. of mercury; the diastolic pressure, 80 mm. The abdomen was pretuberant, measuring 24¼ inches (60 cm.) in circumference. The circumference of the chest was 25½ inches (64 cm.); that of the head was 21 inches (53 cm.). Examination of the genitalia revealed a small penis and small testes which had descended into the scrotum. Rectal examination did not disclose anything palpable that could be identified as the prostate. Axillary and pubic hair

### Laboratory Data

Basal metabolic rates			2/15/40	4/2/40	5/3/40		
Surface area.....			-41%	+7%	+25%		
Body weight.....			-38%	+4%	+26%		
Cholesterol.....			348	263	212		
Thyroid (total received).....			None	53 grains (2.5 Gm.)	113 grains (6.7 Gm.)		
	Hemo- globin	Red Blood Cells	White Blood Cells	Lympho- cytes	Mono- cytes	Neutro- phils	Eosino- phils
2/19/40.....	70%	3.50	7.8	35	6	56	3
5/ 3/40.....	70%	4.16	7.4	42	4	49	5
11/ 6/40.....	86%	5.25	9.8	38	9	51	2
Dextrose tolerance—2 dose, 1 hour test (Exton-Rose method)			Fasting	After ½ Hour	After 1 Hour		
2/16/40.....			67	95	154		
Electrocardiogram							
2/14/40	QRS slurred in all leads; S <sub>1</sub> to 4 present						
	QRS <sub>s</sub> low; T <sub>s</sub> low, diphasic						
10/1/40	R <sub>1</sub> and T <sub>1</sub> higher; S <sub>2</sub> and T <sub>2</sub> deeper and higher						
Miscellaneous data							
Urinalyses, the Kahn serologic test and the Mantoux test (1:1,000) gave negative results							
The values for calcium and for inorganic phosphorus before therapy were respectively							
9.9 mg. and 4.5 mg. per hundred cubic centimeters of serum							

were absent. Psychologic studies made in March 1940 revealed an intelligence quotient of 78, which classified M. B. as a "borderline defective."

*Laboratory Studies.*—Roentgenograms of the wrists and knees taken in February 1940 revealed delayed ossification, the growth corresponding to that of a child 8 or 9 years old. Cross striations indicative of disturbance in growth were noted in the metaphyses. The sella turcica was within normal limits. A complete gastrointestinal study revealed no organic lesions. The colon, after an enema of an opaque substance, showed redundancy and dilatation suggestive of megacolon.

The patient cooperated during determinations of the basal metabolic rate. The laboratory data are presented in the form of a table.

*Subsequent Course.*—M. B. was given 1 grain (0.06 Gm.) of thyroid daily for two weeks; then the dose was increased to 2 grains (0.12 Gm.) daily. Ample vitamins were also prescribed. On June 14, 1940, in a little over three months



(fig. 2), the supraclavicular fat pads had disappeared; the boy had grown  $1\frac{1}{4}$  inches (3 cm.) and lost  $8\frac{1}{2}$  pounds (3.8 Kg.). The abdominal girth had decreased  $3\frac{1}{4}$  inches (8 cm.). His color was better. He was no longer constipated. During this time a number of teeth had erupted. His general reactions and his speech were improved.<sup>2</sup> On October 1 he was no longer recognizable as a cretin; no complaints were present, and he had made a further gain in height of  $1\frac{1}{4}$  inches and regained 6 pounds (2.7 Kg.), a total increase in stature of  $2\frac{3}{4}$  inches in approximately seven and one-half months. On November 6, when last seen, he had gained a further  $2\frac{1}{2}$  pounds (1.2 Kg.).

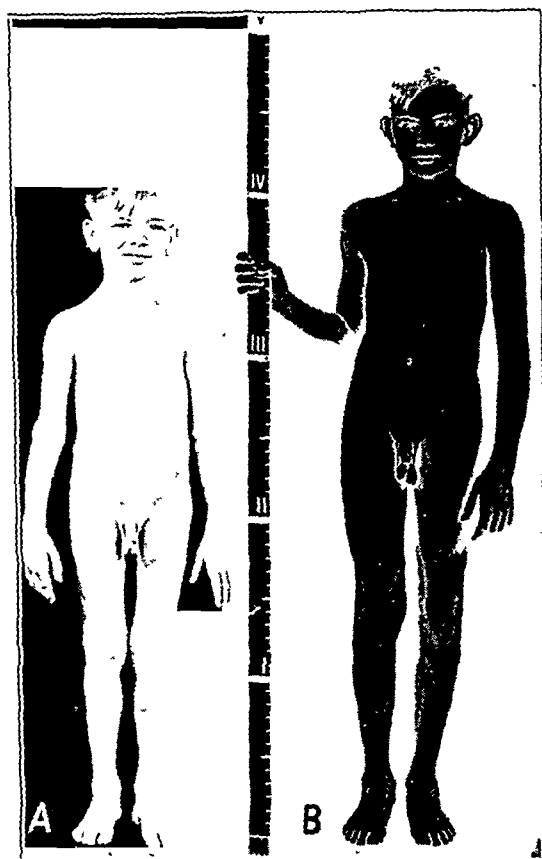


Fig. 2.—M. B. in June 1940 (A), photographed beside a younger brother (B).

#### COMMENT

M. B. was recognized as a cretin at the age of  $2\frac{1}{2}$  years, the symptoms apparently dating from infancy. We cannot be certain that this boy had congenital hypothyroidism. Roentgenograms of the knee at this period, revealing an absence of the distal femoral epiphysis, would have confirmed the diagnosis of congenital hypothyroidism.

2. Schreiber, S. L.; Bronstein, I. P., and Brown, A. W.: Speech Studies in Cretins: Speech Sounds, *J. Nerv. & Ment. Dis.* **92**:169 (Aug.) 1940.

Whether pertussis at the age of 6 months played a part in the picture is questionable. We have had a patient with juvenile hypothyroidism who developed normally up to the age of 2 years, at which time she acquired pertussis. From then on her growth and development were greatly retarded, and an erroneous diagnosis of postpertussis encephalitis was made. She improved rapidly with thyroid therapy.

In our experience with cretins we have frequently encountered children who were considerably undersized and whose history revealed inadequate or sporadic treatment with thyroid. Since thyroid deficiency is one of the important factors in the causation of under stature, such children should be studied diagnostically before the possibility of hypothyroidism is dismissed. Frequently the history and the results of physical examination enable the physician to make a correct diagnosis. At times a more comprehensive study may be indicated. Determination of the basal metabolic rate as ordinarily made and interpreted is not satisfactory in the cases of young children. With infants the basal metabolic rate can be determined only by the use of a respiratory chamber, but this is not usually feasible. With older children the basal rates are unreliable because of lack of cooperation. When accurate basal metabolic determinations are difficult to obtain, studies of ossification of the wrist and knee are valuable, marked retardation being associated with cretinism. Hypercholesteremia<sup>3</sup> and decrease or absence of urinary excretion of creatine are also important aids in the diagnosis of hypothyroidism.

In our experience, adequate dosage is determined by physical, osseous and mental growth and by the avoidance of severe toxic symptoms. Since a rigid table of dosage is impracticable, we prescribe the following average doses. This regimen has given satisfactory results in a series of 50 patients with hypothyroidism whom we have had under our care for the past ten years.

<i>Age</i>	<i>Daily dose of thyroid</i>
6 months to 1½ years	½ to 1½ grains (0.03 to 0.09 Gm.)
1½ years to 8 years	1 to 3 grains (0.06 to 0.18 Gm.)
8 years to adolescence	1½ to 3 grains (0.09 to 0.18 Gm.)

Not infrequently it has been necessary for us to employ much larger doses than those mentioned in order to obtain optimal responses.

M. B. did not show any increase in his rate of growth after considerable treatment with an anterior pituitary extract containing the growth-promoting factor, but with ample doses of thyroid he made spectacular progress. We have found thyroid to be a remarkable growth

3. Bronstein, I. P.: (a) Studies in Cretinism and Hypothyroidism in Childhood: Blood Cholesterol, *J. A. M. A.* **100**:60 (May 27) 1933; (b) Hypothyroidism in Children, *Am. J. Dis. Child.* **47**:913 (April) 1934.

stimulant for our patients with hypothyroidism. Persistent, continuous and adequate therapy has resulted in good physical development even when we began treatment as late as 7 years of age.<sup>4</sup> Fair physical development resulted when treatment was started between 7 and 11 years of age. Mental development is dependent on recognition and adequate treatment under the first year.<sup>5</sup>

Anemia is usually a part of the picture of hypothyroidism. M. B. did not respond to large doses of stomach U.S.P. and iron, but his anemia was improved by thyroid therapy.

In those of our patients with hypothyroidism who were children, constipation, a protuberant abdomen and umbilical hernias were constant symptoms. In cases in which roentgenograms of the colon were taken after a barium sulfate enema, megacolon was found. In no instance did we encounter persistence of these symptoms after ample thyroid therapy.

#### CONCLUSIONS

The inadequately treated child with deficiency of the thyroid may present symptoms simulating other conditions and leading to diagnostic errors.

Our patient's symptoms were on the basis of thyroid deficiency and were corrected by adequate thyroid therapy.

The understatured child should have the benefit of a diagnostic study to exclude hypothyroidism.

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4. Bronstein, I. P.: Unpublished data.

5. (a) Bronstein, I. P., and Brown, A. W.: Hypothyroidism and Cretinism in Childhood: Mental Development, *Am. J. Orthopsychiat.* **4**:413 (July) 1934. (b) Brown, A. W.; Bronstein, I. P., and Kraines, R.: Hypothyroidism and Cretinism in Childhood: Influence of Thyroid Therapy on Mental Growth, *Am. J. Dis. Child.* **57**:517 (March) 1939.

# A COMPARISON OF THE EFFECTS OF HEAT AND THOSE OF COLD IN THE PREVEN- TION AND TREATMENT OF SHOCK

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There has been a revival of interest in recent years in the reactions of living matter to changes in temperature. From the therapeutic point of view the effects of fever therapy in the treatment of infections, of low temperatures in the retardation of growth of cancer<sup>1</sup> and of cooling parts with deficient circulation in the prevention of gangrene<sup>2</sup> have been studied. In addition to determining the effects of different temperatures on the local tissues in which the circulation was inadequate, Allen<sup>2b</sup> found that constriction of the circulation of the thigh is more apt to be accompanied with shock if the local temperature is high than if it is low.

Because of the variability in individual responses to various means of producing shock, such as trauma and the removal of blood, it is extremely difficult to compare the effects of various therapeutic agents. In other words, the variation in the individual responses to trauma or bleeding may be greater than the difference in the effects of two methods of therapy. For this reason rather extreme alterations of temperature, both above and below the normal level, have been brought about in order that the difference in effects might be more clearly discernible. It is to

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1. Smith, L. W., and Fay, T.: Temperature Factors in Cancer and Embryonal Cell Growth, *J. A. M. A.* **113**:653 (Aug. 19) 1939.

2. (a) Starr, I., Jr.: On the Use of Heat, Desiccation and Oxygen in the Local Treatment of Advanced Peripheral Vascular Disease, *Am. J. M. Sc.* **187**:498, 1934. (b) Allen, F. M.: Surgical Considerations of Temperature in Ligated Limbs, *Am. J. Surg.* **45**:459, 1939; (c) The Tourniquet and Local Asphyxia, *ibid.* **41**:192, 1938; (d) Effects of Ligations on Nerves of the Extremities, *Ann. Surg.* **108**:1088, 1938; (e) Physical and Toxic Factors in Shock, *Arch. Surg.* **38**:155 (Jan.) 1939. (f) Freeman, N. E.: Influence of Temperature on the Development of Gangrene in Peripheral Vascular Disease, *ibid.* **40**:326 (Feb.) 1940. (g) Brooks, B., and Duncan, G. W.: The Effects of Temperature on the Survival of Anemic Tissue, *Ann. Surg.* **112**:130, 1940.

be understood that the alterations in body temperature were so great in many of the experiments that no conclusions regarding the treatment of shock in man can be drawn. On the other hand, it is believed that the results portray fairly accurately the effects of marked degrees of heat and cold on animals in incipient or fully developed shock.

#### METHODS AND RESULTS

Large animals were used in all experiments, and pain was prevented by the use of various anesthetic agents, the choice of the agent varying with the method used for producing the shock. One of the two methods for producing shock consisted of the removal of blood from the femoral artery. In some experiments blood equaling 3 per cent of the body weight was removed during a thirty minute period, and heat or cold was then applied. In other experiments blood was removed from the control and from the experimental animals until equal declines in the blood pressure (to about 75 mm. of mercury) had been caused, and heat or cold was applied to 1 of the 2 animals. The second method of producing shock consisted of traumatization of one of the posterior extremities of the deeply anesthetized animal. Heat or cold was applied approximately thirty minutes after the cessation of the trauma. A depression of temperature was produced by partially surrounding the animal with rubber bags which contained crushed ice. An elevation of temperature was caused by placing the animal, covered with a blanket, on a metal table which had electric lights encased beneath it. Observations were made of the arterial blood pressure, the pulse rate, the respiratory rate, the hematocrit reading, the rectal temperature and the duration of survival.

*Hemorrhage.*—As has been stated, blood equaling approximately 3 per cent of the body weight was removed in some experiments, while in others sufficient blood was removed to reduce the blood pressure to a given level. Because of the individual variation in susceptibility to hemorrhage, the results of the latter experiments are believed to be the more significant.

(a) Removal of Blood Equal to Approximately 3 per Cent of the Body Weight or Approximately One Third of the Blood Volume: Morphine was used as the anesthetic in these experiments. The blood was removed intermittently over a thirty minute period, and heat or cold was applied, except in the control experiments, approximately thirty minutes afterward. Of the control animals, which totaled 14, 5 recovered, and the average duration of life of the remaining 9 following bleeding was three hours and thirty-three minutes. There were 9 experiments in which, after bleeding, the animals were exposed to heat; the average elevation of the rectal temperature was 3.7 degrees C. (6.6 degrees F.). All of the animals died, the average duration of life being five hours and twenty-nine minutes. There were 8 experiments in which the effects of hemorrhage and cold were studied. The average depression of the rectal temperature was 12.3 degrees C. (22 degrees F.). All of the animals died, the average duration of life being eleven hours and thirty-six minutes. It is to be noted that the application of heat or cold of these rather extreme degrees did not increase the chances of survival. The animals exposed to cold lived twice as long as those exposed to heat.

Transfusions of large quantities of blood were used in the treatment of 4 animals in which the blood pressure had been reduced by bleeding and cold had been

applied. The blood pressure had been at a low level for from two to six hours before treatment by transfusion was begun. Only 1 of the 4 dogs recovered, and, rather strangely, the blood pressure had been at a low level for six hours before the massive transfusion was begun.

(b) Reduction of the Blood Pressure to a Given Level by Hemorrhage: Approximately ninety minutes was allowed for the reduction of the blood pressure to the desired level, which in most instances was about 75 mm. of mercury. The experiments were performed in pairs, dogs of approximately the same body weight and size being used. The blood pressure was reduced by hemorrhage to the same level in the 2 animals; 1 animal was used as a control, and heat or cold was applied to the other. Pentobarbital sodium, 25 mg. per kilogram of body weight, was used as the anesthetic agent in most of the experiments.

Eleven pairs of experiments were performed in which the effects of cold were studied. The average quantity of blood removed from the controls was 2.41 per cent of the body weight, and the amount was 2.73 per cent in the animals subjected to cold. The blood pressure was reduced to approximately 75 mm. of mercury. Comparison of the 11 pairs of experiments shows that the control animal lived longer in 3 instances; the experimental animal (with reduced temperature) survived longer in 7 instances, and the duration of life was the same in 1 pair. One animal in each series recovered. Excluding these, the average duration of life of the controls (after cessation of bleeding) was eleven hours and twenty minutes, and that of the experimental animals, sixteen hours. The reduction of the rectal temperature in the cold group ranged from 3.6 to 7.65 degrees C. (6.4 to 13.7 degrees F.), the average being 5.9 degrees C. (10.6 degrees F.). The results suggest that the reduction of temperature was beneficial from the point of view of increasing the duration of life, but there is no evidence that this procedure increases the likelihood of survival.

Seven pairs of experiments were performed in which the effects of heat were studied. In 6 of the 7 pairs of experiments the animal in which the body temperature was elevated by the application of heat died before the control, and the duration of life was the same in the remaining pair. Two of the control animals recovered. The duration of life of the remaining 5 controls was eight hours and three minutes, whereas that of the 7 animals subjected to heat was three hours and fifty minutes. The blood pressure had been reduced to the same level (approximately 75 mm. of mercury) in the two groups. The elevation of the rectal temperature ranged from 3.2 to 4.3 degrees C. (5.7 to 7.7 degrees F.), the average elevation being 3.8 degrees C. (6.8 degrees F.). The results indicate that the application of heat of this degree decreases both the survival period and the chances of recovery.

*Trauma.*—Pain was prevented by the use of morphine and ether. Eight experiments were performed in which the effects of trauma and exposure to heat were studied, and 15 experiments were carried out in which the effects of trauma and exposure to cold were determined. The local fluid loss was about the same in the two groups but was less than that usually encountered following this type of trauma when neither heat nor cold is applied. The decline of the rectal temperature in the experiments in which cold was applied ranged from 4.4 to 10.7 degrees C. (9 to 19.2 degrees F.), the average being 6.6 degrees C. (11.8 degrees F.). The elevation of temperature in the experiments on heat ranged from 1.6 to 5.6 degrees C. (2.8 to 9.8 degrees F.), the average being 3.6 degrees C. (6.4 degrees F.). The most striking differences in the two groups were that the animals which were exposed to cold lived twice as long (six hours and thirty-five minutes) as did

those exposed to heat (three hours and six minutes) and that 1 of the animals exposed to cold recovered. These experiments simply show that the period of survival following traumatization is usually longer when the temperature is rather markedly depressed than when it is considerably elevated.

One of the most striking differences in the effects of heat and those of cold was found in the length of time for which the blood pressure remained at a low level before death. This was noted both in the experiments on hemorrhage and in the experiments on trauma. When the temperature of the animal was considerably elevated death usually occurred shortly after the critical level was reached or passed. On the other hand, when the temperature of the animal was significantly depressed it was noted frequently that the blood pressure remained at a low level for a number of hours preceding death. The feces during the period of prolonged low blood pressure contained blood. Examination of the intestinal tract subsequently revealed gross hemorrhage. Another observation (and one to be anticipated) was that the venous blood of the animals exposed to cold was unusually bright in color. Determinations of the oxygen content were not performed in our studies but have been reported previously by Goldschmidt and Light.<sup>3</sup>

The effects of local rather than general application of heat and cold were determined in a few experiments. Additional observations are necessary, and they will be reported subsequently.

#### COMMENT

A number of observers have found that vasoconstriction accompanies secondary or hematogenic shock except in the terminal stages. The degree of reduction of the blood flow to all the tissues is not the same. Gesell<sup>4</sup> found that a decrease in the blood volume of less than 10 per cent when produced by hemorrhage may elicit through vasoconstriction of central origin a decreased flow of blood through the submaxillary gland of more than 60 per cent even though accompanied with a rise of blood pressure. The blood flow to the extremities is more greatly reduced in the presence of secondary shock than is that to the more vital structures, such as the brain, heart and adrenal glands. This raises the question of the effects of heat and cold on the partition of the blood flow in shock. Actual measurements are not available, but other observations permit discussion of this point.

Prinzmetal and Wilson<sup>5</sup> found in the normal arm an increase from a blood flow of 1.7 cc. per hundred centimeters per minute in a bath at 24 C. to one of 14.9 cc. in a bath at 45 C. Benson<sup>6</sup> found an increase

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3. Goldschmidt, S., and Light, A. B.: The Effect of Local Temperature upon the Peripheral Circulation and Metabolism of Tissues as Revealed by the Gaseous Content of Venous Blood, *Am. J. Physiol.* **73**:146, 1925.

4. Gesell, R.: Studies on the Submaxillary Gland: IV. A Comparison of the Effects of Hemorrhage and of Tissue-Abuse in Relation to Secondary Shock, *Am. J. Physiol.* **47**:468, 1918.

5. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, *J. Clin. Investigation* **15**:63, 1936.

6. Benson, S.: Volume Changes in Organs Induced by the Local Application of External Heat and Cold and by Diathermy, *Arch. Phys. Therapy* **15**:133, 1934.

in the blood volume of the foot and leg immersed in water at from 40 C. to 47 C. which averaged 2.76 per cent of the volume of the limb. Bazett<sup>7</sup> said that simultaneous heating of the whole surface of the body should increase the blood content of the skin by 0.5 liter or more. In the normal subject this redistribution of the blood volume and the blood flow may occur without resulting harm. When the blood volume is significantly reduced as a result of hemorrhage or trauma, the increase in the blood content of the skin and muscle following the application of excessive heat will be accompanied with a reduction of the blood flow to the more vital structures, and additional harm will ensue. In addition to the vascular dilatation, the blood volume may be further reduced by the development of edema, which occurs more rapidly at the higher temperatures, as was shown by Landis and Gibbon.<sup>8</sup>

The mechanisms involved in the vascular responses to heat and cold were discussed recently by Bazett.<sup>7</sup> That a rise in central temperature may induce vasodilatation is supported by the findings of Gibbon and Landis,<sup>9</sup> who noted vasodilatation in the lower extremities in response to immersion of the forearms in warm water. In our experiments in which heat was applied there was a general elevation of temperature, including that of the internal organs, and there was probably general vasodilatation. In other words, the vasoconstriction of secondary shock was probably replaced by vasodilatation with a reduction in the effective volume of circulating blood.

Another explanation of the beneficial effects of cold has as its basis the reduction of metabolism of tissue. No matter how shock is initiated, the ultimate cause of deterioration is peripheral stagnant anoxia, i. e., lack of sufficient oxygen to maintain life in the cells of vital structures at ordinary temperatures. It is clear that two approaches to this dilemma may be made. The oxygen supply to the tissues can be increased to meet the existing demand, or the demand for oxygen can be reduced to meet the existing supply. Hypothermia, by lowering the rate of metabolism, reduces the tissue requirement for oxygen. As tissue repair (for example, wound healing) occurs during hypothermia, it is possible that a capillary bed damaged by previous anoxia might become sufficiently repaired during prolonged hypothermia to make subsequent measures to restore blood volume and blood pressure by transfusion permanently effective.

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7. Bazett, H. C.: The Effect of Heat on the Blood Volume and Circulation, *J. A. M. A.* **111**:1841 (Nov. 12) 1938.

8. Landis, E. M., and Gibbon, J. H., Jr.: The Effects of Temperature and of Tissue Pressure on the Movement of Fluid Through the Human Capillary Wall, *J. Clin. Investigation* **12**:105, 1933.

9. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, *J. Clin. Investigation* **11**:1019, 1932.



Our results are somewhat similar to those obtained by Allen<sup>2e</sup> in studies in which he constricted the circulation to the thigh. He found that when the ligated parts are refrigerated by being kept immersed in ice water the otherwise surely fatal ligations of the hindlegs for eight hours and of the abdomen for three hours can be carried out safely; that the changes in the blood are minimized, and that recovery occurs.

It should be emphasized that this paper does not offer evidence to the effect that the time-honored custom of warming the patient in shock is a bad one. Neither is it proved (or believed, for that matter) that measures to reduce below normal the body temperature of patients in shock should be instituted. It is shown, at least in animals in shock, that excessive cold is preferable to excessive heat. It should be remembered that in the human being the extremities may be cold in the presence of shock because the inadequate circulation is diverted in part to more important structures and that attempts to warm the skin and adjacent tissues by artificial means may result in further impairment of the circulation to the essential and more easily damaged organs. We believe that the patient in shock should have adequate cover but that more drastic means to elevate the temperature of the skin should be used with great caution, if at all. Much more important than supplying heat artificially is the augmentation of the reduced blood volume by the intravenous introduction of whole blood or plasma.

#### SUMMARY

The effects of causing rather marked elevations or depressions of the body temperature of animals in shock as a result of hemorrhage or trauma have been determined. Significant elevations of temperature decrease the chance of life and shorten the period of survival. The application of cold does not increase the chance of survival but is accompanied with a lengthening of the survival of an animal with a low blood pressure. Significant elevations of temperature cause more disastrous effects than do depressions of similar degree.

## PELVIC ACTINOMYCOSIS

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CHICAGO

In 1934, Cornell<sup>1</sup> reviewed the literature on actinomycosis of the internal female genitalia and found 71 published cases, including those in which the process was listed as parametrial. In 1937, Lisa and Levine<sup>2</sup> found 5 additional cases in the literature and described 1 of their own.

The history usually given is one of a chronic pelvic inflammatory condition, and in most cases it cannot be differentiated from other chronic pelvic inflammatory processes. The diagnosis may be made by examination of the pus obtained at colpotomy. However, in routine examinations the actinomycetes may easily be overlooked. The direct smears may show no evidence of actinomycosis, or the fragments of any hyphae present may easily be mistaken for long bacilli. Aerobic and particularly anaerobic cultures on appropriate mediums should be made. From surgical and autopsy material the diagnosis can be established by the characteristic structure of the ray fungi in the stained sections. Staphylococci may occasionally clump together, forming so-called botryomycetes, and under low magnification these resemble the ray fungus of actinomycosis. However, under high magnification the cocci are easily distinguished from the branched filaments of the ray fungi.

The following 2 cases illustrate the usual chronic clinical course of the disease and the bad prognosis when the process has been present for some time.

The cases are reported with the permission of Dr. Robert Coombs and Dr. Karl Gustin.

### REPORT OF CASES

CASE 1.—A housewife 40 years of age was admitted to the Grant Hospital of Chicago on June 11, 1937. She had borne 1 child, six years previously. She complained of pain in the lower part of the abdomen, with nausea and vomiting. Burning on urination and a vaginal discharge had been present for two months. The white cell count was 30,700 per cubic millimeter of blood, with 90 per

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From the Grant Hospital of Chicago and the Department of Pathology, University of Illinois School of Medicine.

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cent polymorphonuclear leukocytes. A colpotomy was performed, and the material obtained resembled "sawdust in a bloody fluid." The bacterial flora was found to be intestinal in origin, but no particular studies were conducted to culture fungi. Six days after the operation the white cell count was 9,600 per cubic millimeter, with 77 per cent polymorphonuclear leukocytes.

Three months later she returned to the hospital complaining of pain in the lower part of the abdomen. The white cell count at this time was 11,900 per cubic millimeter, with 83 per cent polymorphonuclear leukocytes. In March 1940 both tubes and both ovaries were removed. After the operation the temperature gradually rose to 106 F., and the patient died on the third postoperative day. Permission for an autopsy was not obtained.

The tissue removed at operation consisted of the tubes and ovaries. The left ovary measured 4.5 by 3 by 3.5 cm. The surfaces made by sectioning were pale tan and were mottled with abscesses up to 8 mm. in diameter. The right ovary measured 2 by 2 by 1.5 cm. The surfaces made by sectioning were pale gray and were mottled with irregular yellow areas. The fimbriated end of the left fallopian

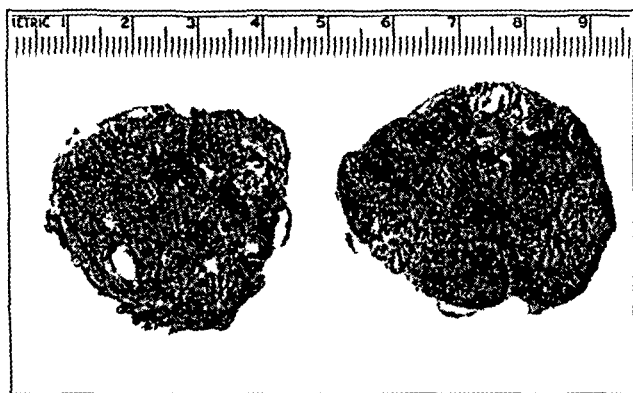


Fig. 1 (case 1).—Cut surfaces of the ovary, with multiple small abscesses.

tube was occluded. The wall was thickened up to 6 mm. The fimbriated end of the right tube was patent, and the wall was thickened up to 4 mm. The microscopic section of the left ovary showed numerous small abscesses. In the center of these abscesses were ray fungi with masses of mycelial threads, typical of actinomycosis. The right ovary showed inflammatory infiltrations but no typical abscesses with ray fungi.

CASE 2.—A housewife 33 years of age was admitted to the Grant Hospital on May 25, 1938. Her illness had begun on Jan. 5, 1936, when a ruptured appendix was diagnosed and conservative treatment was instituted for three weeks, after which a colpotomy was performed at another hospital. She returned several weeks later for an appendectomy. She left the hospital without any drainage.

In May 1936 she complained of pain in the lower part of the abdomen and drainage from the site of the old appendectomy incision. The drainage continued for several months. Flexion of the left leg occurred, and the leg was placed in traction. An abscess in the left side of the pelvis was diagnosed and drained. She was discharged with draining sinuses on the left side. The sinuses closed after six months.

In April 1937 an abscess developed on the inner aspect of her left thigh. In September an abscess developed in the left buttock. In March 1938 all the sinuses stopped draining. The patient complained of a return of abdominal pain. Drainage was instituted again, and the pain ceased. At the time of her admission to the Grant Hospital there were draining sinuses in the left thigh, in the buttocks and over the left anterior superior spine of the ilium. A rectovaginal fistula was present. The liver was enlarged a hand's breadth below the right costal border. The spleen was palpable. Bronchopneumonia developed, and the patient died fifteen days after entering the hospital.

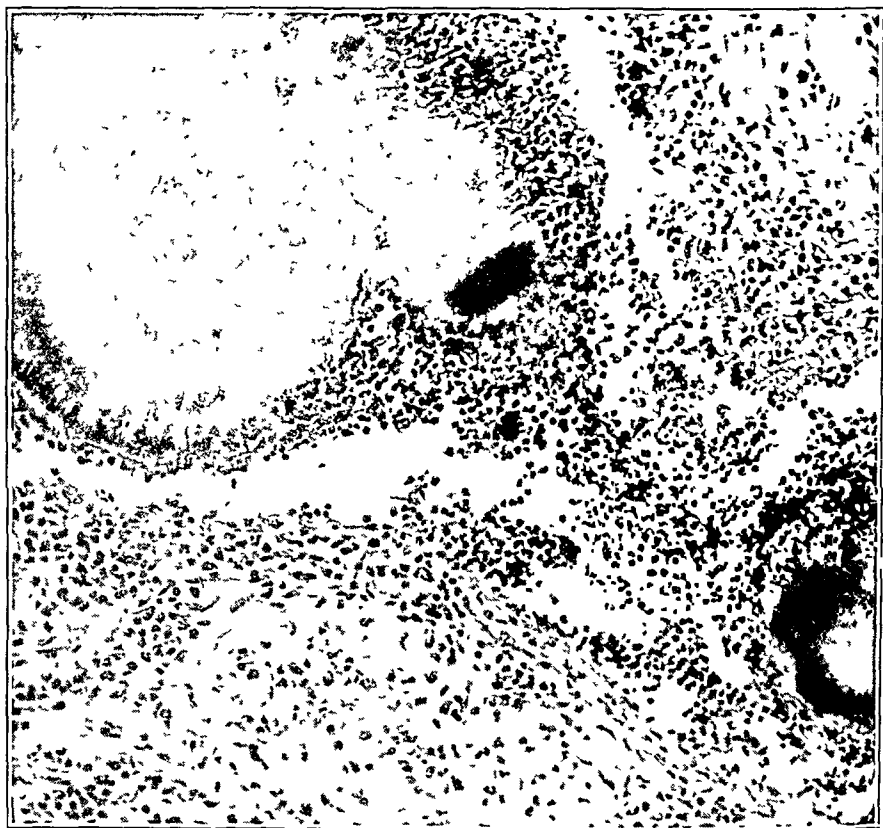


Fig. 2.—Colonies of ray fungi surrounded by pus cells and macrophages.  $\times 112$ .

*Autopsy.*—The anatomic diagnosis was as follows: The pelvic organs were matted together by moderately firm adhesions. When these were broken, pockets of thick purulent material were opened in the cul-de-sac of Douglas and in the parametrial tissue. Beneath the parietal peritoneum on the left side there were purulent infiltrations, and these followed fascial planes and communicated with the sinistral tracts leading to the surface of the skin.

The uterus measured 6 by 4 by 2.5 cm. The endometrium was pale tan and slightly granular. The right ovary measured 6 by 4 by 4 cm. The surfaces made by sectioning were pale yellow and were mottled with irregular soft brown areas measuring up to 8 mm. Some of these areas were confluent. The right fallopian

tube could not be recognized grossly. The adnexal structures on the left were prolapsed and adherent by dense adhesions to the rectum. The liver weighed 4,250 Gm., and the surfaces made by sectioning were mottled with yellow-gray, soft areas measuring up to 5 mm. in diameter. Many of these areas coalesced to form irregular formations. Pale yellow pus could be expressed from these areas. The spleen weighed 590 Gm., and the trabeculae were very distinct. Microscopic examination of the liver and the right ovary showed abscess formation with the characteristic ray fungi.

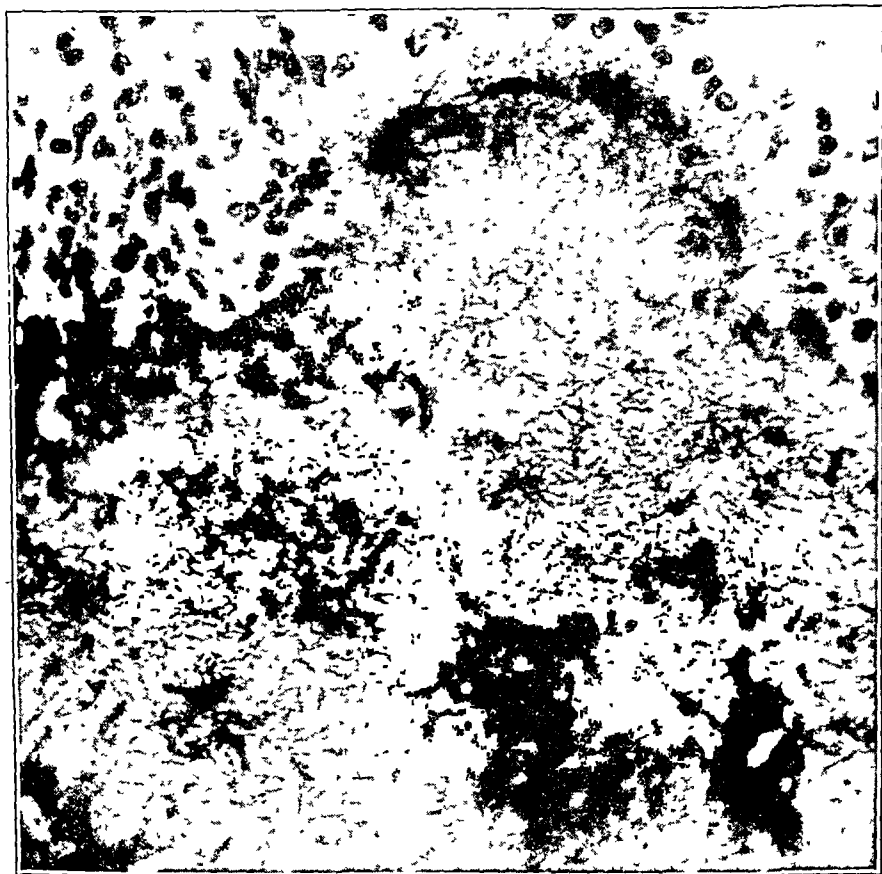


Fig. 3—Ray fungus, showing the feltlike branching mycelia. Gram-Weigert stain;  $\times 600$ .

#### COMMENT

In most of the reported cases the ovaries, fallopian tubes and parametrial tissue were involved. These structures are usually involved secondarily from the cecum or the appendix. In the presence of a chronic pelvic inflammatory condition the history of a previous appendical abscess suggests the possibility of an actinomycotic infection. Draining sinuses are suggestive. The infection spreads from the region of the cecum or the appendix either intraperitoneally or extraperitoneally

to involve the ovaries or the parametrial structures. According to Blasek,<sup>3</sup> the initial lesion in the intestinal tract may be difficult to locate.

The right ovary is most frequently involved. Falls<sup>4</sup> reported a case of an ovarian abscess with actinomycotic involvement. He stated that only 3 cases of primary ovarian involvement have been reported and that it is very rare for the infection to originate in the uterus, ovaries or tubes and then spread to the ovary. Jaffé<sup>5</sup> discussed the literature on primary actinomycosis of the uterus. The infection followed injuries due to pessaries, abortions and, in 1 instance, prolapse of the uterus.

Hall<sup>6</sup> recently summarized the accepted postoperative treatment. Roentgen treatments are of value, as is the use of iodides and perhaps of thymol. Schuchardt<sup>7</sup> reported the use of a vaccine in the treatment of actinomycosis.

Walker<sup>8</sup> reported a clinical cure after the use of sulfanilamide in the case of a young man with abdominal actinomycosis following rupture of the appendix. Miller and Fell<sup>9</sup> reported encouraging results with sulfanilamide in a boy 11 years of age with actinomycosis involving the lower abdominal wall. Recently, Ogilvie<sup>10</sup> reported marked clinical improvement following the use of sulfapyridine in the case of a young woman with actinomycosis of the lower abdominal wall.

#### SUMMARY

Two cases of pelvic actinomycosis are reported. They illustrate the chronic and serious nature of the disease. One of the patients died a few days after operation; the other had multiple draining sinuses and abscesses of the liver. Recent favorable reports in the literature on the treatment of actinomycosis with sulfanilamide and sulfapyridine may alter the serious prognosis.

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# BASIS AND TREATMENT OF CALCIFICATION OF TENDINOCAPSULAR TISSUES, ESPECIALLY THE SUPRASPINATUS TENDON

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Much has been written regarding the treatment of calcification of tendinocapsular tissues, especially in the region of the supraspinatus tendon.<sup>1</sup> Little attention, however, has been paid to the question of the cause of this abnormal deposition of calcium. Most writers support

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The alpha tocopherol acetate used in this study was supplied by Hoffmann-La Roche, Inc.

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(Footnote continued on next page)

the idea that trauma is the main causative agent. We felt it difficult to accept this opinion, since our experience included several subjects presenting multiple widespread areas of calcification without any clearcut evidence of trauma (accompanying illustration). In fact, it appears that calcification of the tendinocapsular tissues may be the result of a general disorder, possibly metabolic, and that any traumatic influence present merely precipitates the onset of local symptoms.<sup>2</sup>

Along these lines we noted the interesting experiments of Goettsch and Pappenheimer, Evans and others, which showed the production of degeneration, necrosis and calcification of voluntary muscle fibers in certain animals fed a diet deficient in vitamin E.<sup>3</sup> Recently, additional

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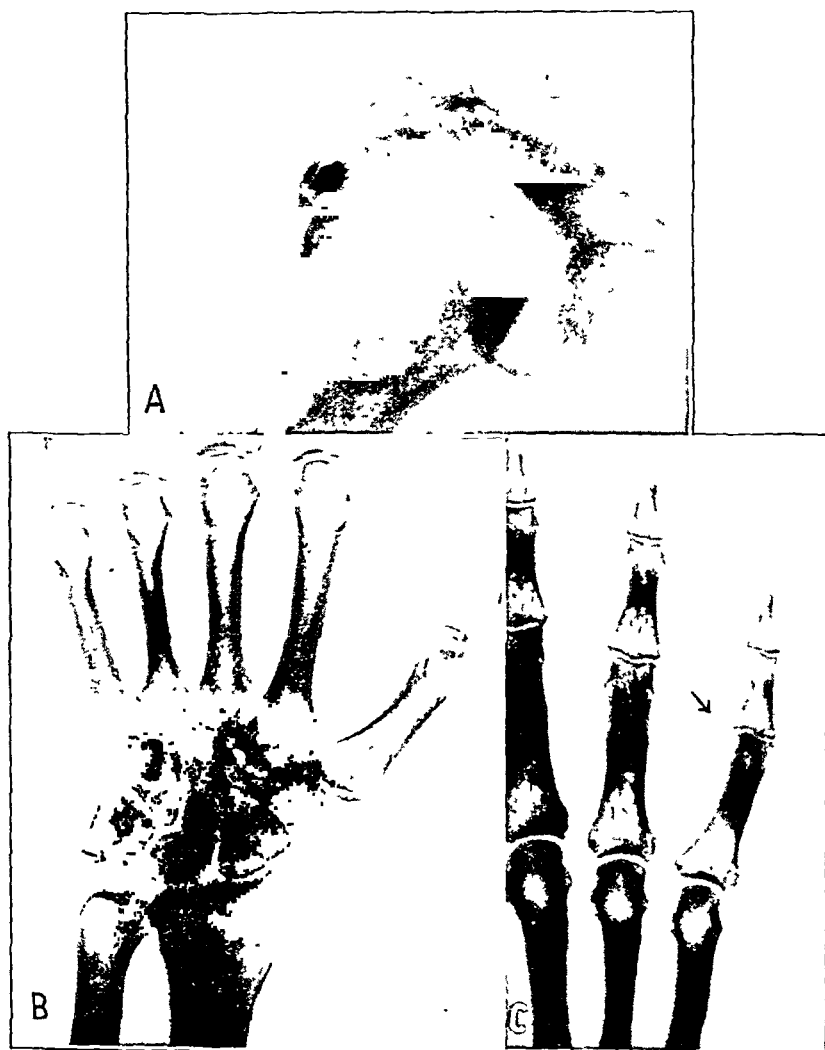
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experiments, performed by Telford, Emerson and Evans, have shown that abnormal changes may be present in the voluntary muscles of ani-



Roentgenograms showing calcification (a) of the right supraspinatus tendon; (b) of the left flexor carpi ulnaris tendon, and (c) of the capsule of the proximal interphalangeal joint of the right little finger. These conditions were present simultaneously in a woman 44 years old.

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mals deficient in vitamin E even when there are few abnormal signs.<sup>4</sup> Furthermore, it was found that the addition of vitamin E in sufficient doses prevented these abnormal alterations in the muscles.<sup>5</sup>

On this basis it seemed worth while to study the effects of administration of synthetic vitamin E (alpha tocopherol acetate) to patients suffering from calcification of tendinocapsular tissues, particularly in the area of the supraspinatus tendon.

#### PROCEDURE

Thirty-four patients complaining of pain in the shoulder area were studied; 21 of these presented acute symptoms, and 13 had prolonged or chronic complaints. Fourteen of the patients were men, and 20 were women. The youngest was 33 years of age, and the oldest was 68. Roentgen examination was made of both the right and the left shoulder in most instances. If pain was present in any joint besides the shoulder, additional roentgenograms were ordered. Each patient followed in this study showed roentgen evidence of calcification in the tendinocapsular tissues of at least one shoulder. Inquiries were made as to the existence of trauma and as to the dietary habits. Only 2 of the 34 subjects gave a definite history of trauma, and 9 subjects gave evidence of dietary deficiency.

Twenty-one of the 34 patients complained of acute local pains and pronounced restriction in motion of the affected shoulder. Five of these 21 subjects showed, in addition, symptomless calcification in the tendinocapsular tissues of the opposite shoulder. One patient presented, together with calcification in the supraspinatus region, similar depositions in the flexor carpi ulnaris tendon and in the capsule of the proximal interphalangeal joint of one of the fingers.

Eight of these 21 patients received vitamin E in the form of alpha tocopherol acetate given by mouth. No immobilization, physical therapy or exercise was employed. Four of these patients received alpha tocopherol acetate in doses from 5 to 20 mg. per day over a period of twenty to fifty-one days. The remaining 4 received 50 to 100 mg. daily for seven to twenty-one days.

Thirteen of the 21 patients with acute symptoms were followed as controls. Some received codeine sulfate; others, lactose; others, injections of vitamin B<sub>6</sub>, and still others, local injections of procaine hydrochloride.

The second group, presenting the chronic condition, consisted of 13 patients who showed calcification of tendinocapsular tissues in at least one shoulder, with a history of chronic symptoms for periods ranging from one month to twenty years. In some, active movements in the affected shoulder were only slightly limited. They had all received previously some form of therapy, consisting of local diathermy, local application of infra-red rays or local infiltration with procaine hydrochloride solution. Three of the 13 had symptomless calcification of the

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showed no change in size. It is of interest to note that in this group of 13 control patients with acute symptoms there were 4 with symptomless calcification of the tendinocapsular tissues of the opposite shoulder. In 1 of these 4 calcification on the painless side disappeared in eleven days, while on the painful side it did not completely resolve. In another the painless calcic area diminished in size in four weeks. In the remaining subject no alterations were observed in the size of the calcic deposition.

In the chronically affected group, consisting of 13 patients, 8 received alpha tocopherol acetate without any other form of treatment. Most of these patients complained only of mild pain and presented little or no limitation in motion. There was subjective improvement within twenty to sixty days with ingestion of alpha tocopherol acetate. Slight changes occurred in the appearance of the calcific deposits as noted on roentgen examination. In no case, however, did the mass completely disappear. No effect was noted on the calcic deposits in the opposite, painless shoulder.

In the group of 5 control patients (with chronic symptoms) for whom the therapeutic regimen consisted of intensive local application of diathermy or oral administration of sedatives and acetylsalicylic acid, only 3 showed signs of improvement after intervals ranging from twenty to sixty days from the beginning of the therapy. In only 1 instance in which acetylsalicylic acid was administered was there roentgen evidence of disappearance of the calcic deposits. In 2 instances in this group of 5 control cases, in which calcification was present in the opposite shoulder, the administration of acetylsalicylic acid had no effect on the roentgen appearance of the calcic mass.

#### COMMENT

This study suggests that the painful, acute phase of calcification of the tendinocapsular tissues is a complication and not a part of the syndrome per se. Treatment directed toward the relief of pain does not necessarily influence the fundamental processes which produce calcification on the tendinocapsular tissues. We observed that any reasonable type of treatment is associated with a symptomatic improvement in the acute phase. Also, the deposit of calcium may completely disappear during or after the acute episode without the intervention of physical therapy, roentgen therapy, aspiration, irrigation or any special medication. In the chronic form of the condition the administration of alpha tocopherol acetate did not alter specifically the clinical picture, nor did it affect the roentgen appearance of the calcific shadow.

As yet the cause of calcification of tendinocapsular tissues is unknown. However, there is a likelihood that deficiency in either intake or absorption of vitamin E may play a part in the production of the necrosis and subsequent calcification of tendinocapsular tissues.

Recent experimental and clinical data clearly show that deficiency of vitamin E may exist in spite of an adequate diet, partly because of poor absorption from the gastrointestinal tract.<sup>6</sup> Furthermore, experimental evidence is at hand to show that changes may exist in voluntary muscles even when the animals present minimal clinical evidence of vitamin E deficiency.

In man the supraspinatus tendon and its contiguous tissues as well as the gluteus medius tendon undergo degenerative changes with advancing age. Yet in a study of 100 shoulders removed post mortem in which degenerative changes were noted in the supraspinatus tendon and the contiguous capsular tendons no evidence of calcification was found.<sup>7</sup> The calcic deposition as seen in the supraspinatus tendon is not ordinarily the result of the changes associated with senile degeneration.

We suspect that the changes and the subsequent calcification in tendinocapsular tissue, as they occur in the supraspinatus tendon, for example, may be the result of vitamin E deficiency. Furthermore, calcification of the tissues in question may produce an acute, painful inflammatory reaction by rupturing into a contiguous bursa or tendon sheath. This reaction usually helps in the resorption of the calcic particles, irrespective of the type of therapy. While the ingestion of alpha tocopherol acetate has no special effect on the already calcified tissues, it may influence the noncalcified necrotic tissue. It is suggested that the administration of vitamin E may be of aid in preventing calcification of necrotic tendinocapsular tissue as it occurs in the supraspinatus tendon.

#### SUMMARY

Calcification of tendinocapsular tissues may be present without any accompanying signs or symptoms. Such calcification may be complicated by an acute episode of pain and tenderness. After this the calcification may disappear with or without medication or local physical therapy. In cases of chronic calcification it seems that the ingestion of alpha tocopherol acetate results in subjective improvement only.

Deficiency in vitamin E may lead to necrosis of tendinocapsular tissues with subsequent calcification. The ingestion of vitamin E does not have a specific effect on the deposited calcium. There is likelihood, however, that the administration of vitamin E may prevent the calcification of necrotic tendinocapsular tissue.

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# RENAL BLOOD FLOW AND SYMPATHECTOMY IN HYPERTENSION

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The importance of the kidneys in the pathogenesis of arterial hypertension has been widely recognized since the demonstration by Goldblatt and his co-workers<sup>1</sup> that lasting hypertension can be produced experimentally by partial constriction of one main renal artery. Page has obtained similar hypertension by compression of the renal parenchyma in the scar of cellophane or silk perinephritis.<sup>2</sup> Although several cases of hypertension in human beings have been described in which the condition arose as the apparent result of partial obstruction of renal circulation or as the result of perinephritis, neither abnormality of the large renal vessels nor diffuse perinephritis is commonly present. Lesions of the small renal arterioles, however, are evident even in the early stages of the disease.<sup>3</sup> It has therefore been suggested that hypertension may ordinarily arise as the result of spasm and sclerosis of the renal arterioles, functional equivalents of the application of myriads of minute intrarenal clamps.<sup>4</sup>

Independently of these observations, repeated clinical experience has shown that an abdominal sympathectomy, such as subdiaphragmatic splanchnic resection with removal of the upper two lumbar sympathetic ganglions and the intervening chain,<sup>5</sup> transdiaphragmatic splanchnic

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From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital.

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4. Goldblatt, H.: Studies on Experimental Hypertension: V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann. Int. Med.* **11**:69, 1937.

5. Craig, W. M., and Adson, A. W.: Hypertension and Subdiaphragmatic Sympathetic Denervation, *S. Clin. North America* **19**:969, 1939.

removal of the lower dorsal and upper lumbar sympathetic chains with their ganglions and communicating rami,<sup>6</sup> bilateral supradiaphragmatic splanchnic section with lower dorsal ganglionectomy<sup>7</sup> or section of the thoracic and upper lumbar anterior nerve roots,<sup>8</sup> results in lowering of arterial pressure, recession of symptoms and slowing of the progress of the disease in many cases of hypertension in man.

The area deprived of sympathetic innervation by these operations includes the kidneys. Since it has been repeatedly shown that renal hyperemia may follow renal denervation in acute experiments in anesthetized animals or in animals recovering from anesthesia, it seemed logical to some to attribute the beneficial effects of sympathectomy to an increase of renal blood flow, although evidence of such a factor was lacking.

The purpose of the present report is to record observations on renal blood flow and hemodynamics in 2 cases of hypertension treated by Smithwick's method of abdominal sympathectomy.

#### METHODS

Nearly all the diodrast which enters the kidney in the blood plasma is removed from the blood during its renal passage. It is excreted largely as the result of chemical transfer (secretion) across the cells into the lumens of the proximal convoluted tubules. The plasma clearance of diodrast (volume of plasma equivalent to one minute's urinary excretion of the dye) is therefore nearly equal to the rate of renal plasma flow, so that if both the plasma diodrast clearance and the hematocrit index are known the approximate rate of blood flow to renal excretory tissues may be calculated.<sup>9</sup>

Inulin appears in the urine solely as the result of filtration through the glomerular capillaries and, unlike urea, is not reabsorbed in the tubules. The inulin clearance (volume of plasma equivalent to one

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6. Smithwick, R. H.: A Technic for Splanchnic Resection in Hypertension, *Surgery* **7**:1, 1940.

7. Peet, M. M.: The Surgical Treatment of Hypertension, *Proc. California Acad. Med.* **5**:58, 1935-1936.

8. Adson, A. W., and Brown, G. E.: Malignant Hypertension: Report of a Case Treated by Bilateral Section of Anterior Spinal Nerve-Roots from the Sixth Thoracic to the Second Lumbar Inclusive, *J. A. M. A.* **102**:1115 (April 7) 1934. Page, I. H., and Heuer, G. J.: A Surgical Treatment of Essential Hypertension, *J. Clin. Investigation* **14**:22, 1935.

9. Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, *J. Clin. Investigation* **17**:263, 1938. White, H. L., and Heinbecker, P.: Interpretation of Diodrast in the Dog, *Proc. Soc. Exper. Biol. & Med.* **43**:7, 1940. Corcoran, A. C.; Smith, H. W., and Page, I. H.: Renal Excretion of Diodrast in the Dog, *Am. J. Physiol.* **129**:P338, 1940.

minute's urinary excretion of inulin) is therefore equivalent to the volume of water removed from the plasma by glomerular filtration. The ratio of inulin to diodrast clearance has been termed "filtration fraction" and is a measure of the proportion of water removed from plasma by glomerular filtration. The value of this ratio increases with increasing intraglomerular pressure, since increased pressure forces more water through the glomerular capillaries. Intraglomerular pressure, and with it the filtration fraction, may be increased either by dilation of the afferent arterioles (forward pressure on the glomerular capillaries) or by constriction of the efferent arterioles (back pressure on the glomerular capillaries). Dilation of the afferent arterioles would increase the renal blood flow and the filtration fraction, while constriction of the efferent arterioles would increase the filtration fraction and at the same time tend to decrease the renal blood flow. An increased filtration fraction and a decreased renal blood flow characterize the renal changes observed in most cases of hypertension in human beings.<sup>10</sup> These abnormalities are probably the expressions of efferent arteriolar constriction.

Simultaneous measurements of diodrast and inulin clearances permit the calculation of effective renal blood flow and indicate the site and degree of arteriolar vasoconstriction. Since the renal vasoconstriction associated with hypertension is predominant in the efferent arterioles, the hypothetic vasodilation which might follow denervation as the result of sympathectomy would be expected to release this spasm, so that the renal blood flow (diodrast clearance) would increase, while the filtration fraction would return toward normal (0.16 to 0.20). Such a change would suggest that the operation does indeed reverse the renal abnormality of hypertension and, if it is assumed that renal arteriolar spasm is the cause of hypertension, would lead to the conclusion that the primary functional lesion of hypertension can be removed by sympathectomy. That this is probably not the case is shown by the data in the accompanying table.

The measurement of plasma diodrast clearance in the cases reported here was made by a modification of the methods described by Smith, Goldring and Chasis; the determination of diodrast in the plasma and in the urine was made by a modification of the method of White and Rolf,<sup>11</sup> and the inulin analyses were performed by our own method.<sup>12</sup>

10. Smith, H. W.: *Studies in the Physiology of the Kidney*, The Porter Lectures, Publication of the University Extension Division, University of Kansas, Lawrence, Kan., 1939.

11. White, H. L., and Rolf, D.: A Rapid Micro-Method for Determining Diodrast and Inorganic Iodide Iodine in Blood and Urine, *Proc. Soc. Exper. Biol. & Med.* **43**:1, 1940.

12. Corcoran, A. C., and Page, I. H.: Applications of Diphenylamine in the Determination of Levulose in Biological Media: I. The Determination of Inulin; II. The Determination of Levulose in Blood, *J. Biol. Chem.* **127**:601, 1939.



## REPORT OF CASES

CASE 1.—C. H., a man aged 39 years, had hypertension dating from the second of two examinations for life insurance in 1927. The patient was again observed because of headache and fatigability in 1932. His blood pressure at that time was 190 systolic and 110 diastolic. During a period of unusual stress in his work in September 1936 he suddenly had partial right hemiplegia and aphasia, the residues of which had entirely disappeared at the end of two weeks. The blood pressure on the day of the attack was 178 systolic and 130 diastolic. A similar, though less intense, episode occurred in April 1937. Sympathectomy was advised at that time but was postponed for a trial of sodium thiocyanate therapy, for which purpose he was referred to the Lilly Laboratory for Clinical Research. During a six month period of observation without thiocyanate the blood pressure averaged 180 systolic and 130 diastolic, while during the first seven months of treatment the plasma

*Data in Two Cases of Hypertension*

Case	Date	R. B. F.	D. C.	I. C.	F. F.	B. P., Mm. Hg
1	9/27/39	543	310	69	0.225	144/108 (recumbent)
	10/10/39	Unilateral sympathectomy (right side)				
	10/31/39	Unilateral sympathectomy (left side)				
	1/ 5/40	390	220	61	0.275	158/118 (recumbent) 118/ 96 (standing)
2	5/15/40	779	451	95	0.21	228/146 (recumbent)
	6/ 5/40	Unilateral sympathectomy (right side)				
	6/25/40	745	405	94	0.23	198/130 (recumbent)
	10/22/40	840	436	92	0.215	230/120 (recumbent)
	11/28/40	715	379	78	0.206	216/128 (recumbent)
	12/ 5/40	Unilateral sympathectomy (left side)				
	1/ 3/41	642	380	74	0.194	200/130 (recumbent) 112/ 96 (standing)
	3/ 6/41	597	346	76	0.217	192/118 (recumbent) 82/ 48 (standing)

The abbreviations used in this table are as follows: R. B. F., effective renal blood flow calculated from plasma diodrast clearance (D. C.) in cubic centimeters per minute; I. C., plasma inulin clearance in cubic centimeters per minute; F. F., filtration fraction (I. C./D. C.); B. P., blood pressure taken with the patient at rest.

thiocyanate content averaged 7 mg. per hundred cubic centimeters and the blood pressure 160 systolic and 116 diastolic. At this time he was clinically improved and his only complaint was fatigability. In August 1939 it was noted that the thiocyanate seemed to be losing its effect, since the thiocyanate content of the plasma had been maintained at a mean level of 5.8 mg. per hundred cubic centimeters and the blood pressure had averaged 175 systolic and 124 diastolic during the previous three months. Sympathectomy was advised, and he was admitted to the ward for study in September 1939.

During hospitalization he was observed to be emotional, introspective and apprehensive. There was slight (1 plus) constriction of the retinal arterioles. The blood pressure after three days of rest in bed was 144 systolic and 108 diastolic. The renal blood flow was determined (table), and he was referred to Dr. R. H. Smithwick for operation.

The operation consisted of bilateral resection of the sympathetic trunks interrupting the communicating rami of the ninth, tenth, eleventh and twelfth dorsal and the first lumbar segments, with removal of the sympathetic trunks and ganglia from these areas. The great splanchnic nerves were removed from their insertions

over virtually their entire lengths, i. e., to the midthoracic level (sixth dorsal). The two sides were treated separately, the right side on October 10 and the left on October 31. Convalescence was unusually prolonged. The patient was depressed, and the extensive physiologic changes wrought by the operation were reflected in tachycardia even when he was at rest in the horizontal position. There were severe orthostatic hypotension and rapid collapse on standing, so that it was necessary to bandage both legs to the groins and to fit an elastic girdle and an abdominal sponge rubber pad in order to maintain the desired level of blood pressure in the erect posture.

Eight weeks after the operation he was readmitted to the ward of the Lilly Laboratory for Clinical Research for observation and for determination of the renal blood flow. He has had few complaints since this time. The abdominal pad and girdle, the thigh bandages and finally the bandages over the lower part of the legs were successively discarded during February and March 1940. The average blood pressures during the first six months of 1940 were 155 systolic and 108 diastolic (horizontal) and 134 systolic and 114 diastolic (standing). In the last six months of 1940 the blood pressures were 141 systolic and 100 diastolic (horizontal) and 134 systolic and 108 diastolic (standing). Subjectively he is improved as the result of the operation and, although he remains easily upset, is constantly reassured by his feeling of well-being.

CASE 2.—L. D., a man aged 39 years, also was first recognized to have hypertension in a routine insurance examination, in 1929. There were no symptoms of any kind and no subsequent determinations of blood pressure until 1936, when the patient began to suffer from attacks of "inward nervousness," associated with nausea and vomiting. Latent syphilis was discovered at this time; antisyphilitic treatment was instituted in 1937, when he first came under our observation, and continued to 1939. The blood pressure varied widely from 140 systolic and 90 diastolic to 236 systolic and 140 diastolic, although during prolonged rest in bed it averaged 196 systolic and 126 diastolic. Varying degrees (1 plus to 3 plus) of constriction of the retinal arterioles were reported at different times. Attacks of nervousness and vomiting with wide variations of blood pressure continued under treatment with sedatives and suggestion, and it was considered that the patient presented many of the characteristics of the hypertensive diencephalic syndrome.<sup>13</sup> Sympathectomy was advised, partly on the ground that his condition seemed neurogenic. The renal blood flow was determined before the first stage of the operation and after recovery from violent gastrointestinal upsets which followed this intervention. The wound healed slowly, and the second stage (left side) was performed five months after the first. Both operations were done by Dr. E. V. Hahn according to the method of Smithwick.

*Comment.*—The clinical result of the operation in case 1 seems satisfactory, and, although insufficient time has elapsed to justify a prognosis of the ultimate effects of the operation in case 2, it seems not unlikely that the result will be nearly as good, since the maximum level of blood pressure with the patient in the horizontal position is no higher than it was before and with the patient in the erect posture is a great deal lower. Nevertheless (table) there is no evidence of increased renal blood flow. Renal blood flow has, on the contrary, decreased definitely in

13. Page, I. H.: A Syndrome Simulating Diencephalic Stimulation Occurring in Patients with Essential Hypertension, *Am. J. M. Sc.* **190**:9, 1935.

case 1 and slightly in case 2. The decreased renal blood flow in case 1 is accompanied with an increase of the filtration fraction, probably the result of increased efferent arteriolar constriction.

#### GENERAL COMMENT

The results in these 2 cases indicate that radical sympathectomy which includes the sympathetic innervation of the kidneys does not cause renal vasodilatation or relaxation of the abnormal constriction of the glomerular efferent arterioles, even in cases in which strong neurogenic and emotional factors seemed to be operating. Similar observations have been reported by Alving, Adams and Grimson.<sup>14</sup>

Sympathectomy for hypertension was, as has been noted, developed independently of considerations of renal blood flow and, as a procedure, depends neither in theory nor in practice on the production of renal hyperemia. The view that the effects of sympathectomy in cases of hypertension result from increased renal blood flow is based on the renal hyperemia which follows renal denervation in acute experiments in traumatized animals; it entirely neglects chronic experiments, which have shown that renal denervation by section of renal nerves in dogs<sup>15</sup> and in man<sup>16</sup> or by interruption of the sympathetic nervous system in man<sup>17</sup> have no effect on the rate of renal blood flow. Indeed, it has been suggested<sup>18</sup> that the renal vasomotor nerves are normally at rest but that emergencies incident to experimental procedures excite them to cause renal vasoconstriction. Section of the renal nerves provokes transient hyperemia under such conditions. It is therefore not surprising that sympathectomies which involve renal nerves do not affect the renal blood flow in chronic experiments or in the surgical treatment of hypertension. Renal denervation alone, without section of splanchnic visceral nerves, is ineffective in the treatment of hypertension,<sup>16</sup> although the operation, if it depended on a renal effect, should be restricted to the renal nerves.

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14. Alving, A. S.; Adams, W.; Grimson, K. S.; Scott, C., and Sandiford, I.: The Effect of Bilateral Sympathectomy on the Cardio-Renal System in Essential Hypertension, *Proc. Centr. Soc. Clin. Research* **13**:39, 1940.

15. Rhoads, C. P.; Van Slyke, D. D.; Hiller, A., and Alving, A. S.: The Effects of Novocainization and Total Section of the Nerves of the Renal Pedicle on Renal Blood Flow and Function, *Am. J. Physiol.* **110**:387, 1934.

16. Page, I. H., and Heuer, G. J.: The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, *J. Clin. Investigation* **14**:27, 1935.

17. Page, I. H., and Heuer, G. J.: The Treatment of Essential and Malignant Hypertension by Anterior Nerve Root Section, *Arch. Int. Med.* **59**:245 (Feb.) 1937.

18. Smith, H. W.: Physiology of the Renal Circulation, in *Harvey Lectures*, 1939-1940, Baltimore, Williams & Wilkins Company, 1940, p. 166.

Increased urea clearance has been noted at varying intervals after operation<sup>19</sup> in hypertensive patients treated by supradiaphragmatic splanchnicectomy and has been interpreted as evidence of increased renal blood flow. Page and Heuer,<sup>20</sup> however, failed to observe a significant change of urea clearance in patients treated by stripping the renal pedicle (renal denervation), by supradiaphragmatic splanchnic section or by extensive section of the anterior nerve roots. In this connection it should be noted that urea clearance is not a close measure of renal blood flow in the presence of hypertension, since efferent arteriolar constriction increases the proportion of urea removed from the blood. Consequently, although the volume of blood which perfuses the kidneys in the presence of hypertension may be decreased, relatively more urea is removed from it, so that urea clearance is maintained at normal levels until a serious reduction of renal blood flow has occurred. A slight increase of urea clearance is therefore consistent with unchanged or even decreased renal blood flow, since it may express increased efferent arteriolar constriction.

There remain for discussion (*a*) the question of what is the basis of the good results of sympathectomy, since it appears not to be due to improvement in renal circulation, and (*b*) the question of the nature of the renal vasoconstriction associated with hypertension, since it appears not to be neurogenic.

(*a*) The splanchnic vasomotor nerves of man, in contrast to the renal vasomotor nerves, are normally highly reactive in constant adjustments to changes of position, to ingestion of food and to even mild exercise. Especially, the assumption of the erect posture places heavy demands on the competency of this circulation. If it were supposed that interruption of the splanchnic visceral innervation reduces arterial pressure in the presence of hypertension solely by causing arteriolar vasodilation and thus increasing the volume of distribution of blood, it would be difficult to explain a prolonged reduction of arterial pressure, since blood volume usually adjusts rapidly to the space in which it circulates (e. g., amputation at the thigh; adjustment to extremes of heat). Such pooling of the blood should also result in congestion, with attendant digestive disturbances. It appears, therefore, that interruption of visceral innervation decreases arterial pressure by some means apart from arteriolar vasodilation. A clue to the nature of the reduction in arterial pressure is provided by the phenomena which follow successful splanchnic section, namely, tachycardia and hypotension, manifestations of decreased cardiac

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19. Peet, M. M., and Wood, W. W.: The Surgical Treatment of Hypertension: Results in Three Hundred and Fifty Consecutive Cases Treated by Bilateral Supradiaphragmatic Splanchnicectomy and Lower Dorsal Sympathetic Ganglionectomy, *J. A. M. A.* **115**:1875 (Nov. 30) 1940.

20. Page, I. H., and Heuer, G. J.: The Effect of Splanchnic Nerve Resection on Patients Suffering from Hypertension, *Am. J. M. Sc.* **193**:820, 1937; footnotes 16 and 17.

output, more or less intensely manifest in the erect posture. A study of the effects on circulation of spinal anesthesia in normal human beings by Smith, Rovenstine, Goldring, Chasis and Ranges<sup>21</sup> has shown that spinal anesthesia causes postural hypotension by permitting postarteriolar dilation of capillaries, venules and veins, thus decreasing venous return and cardiac output, notably in the erect posture. This effect of spinal anesthesia is not associated with renal arteriolar changes and may be explained as the result of postarteriolar dilation of veins, venules and, possibly, capillaries. Consequently, although spinal anesthesia is not in all respects similar to extensive sympathectomy, the fall of arterial pressure in hypertensive patients treated by such methods as anterior nerve root section may in part be the result of postarteriolar dilation with decreased venous return. Clearly, the heart cannot maintain greatly increased arterial pressure if the venous supply of blood is inadequate. Added to this mechanism there is the factor of inadequate splanchnic constriction in response to the stimulation of the erect posture. The effects on circulation of postarteriolar vasodilation and of the failure of arteriolar adjustments to posture are, of course, most evident in the erect posture.

This explanation of the reduction of arterial pressure by sympathectomy is supported by numerous observations that interruption of the sympathetic nervous system in dogs suffering from renal hypertension by renal denervation,<sup>22</sup> splanchnic resection,<sup>23</sup> anterior nerve root section,<sup>24</sup> total sympathectomy<sup>25</sup> or even destruction of the spinal cord<sup>26</sup> has little or no effect on the level of arterial blood pressure, while such operations, renal denervation excepted, cause reduction of arterial pressure in hypertensive man. This difference between man and experimental animals has been interpreted as evidence of a neurogenic origin

21. Smith, H. W.; Rovenstine, E. A.; Goldring, W.; Chasis, H., and Ranges, H. A.: The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arterioles and Especially Those of the Renal Circulation, *J. Clin. Investigation* **18**:319, 1939.

22. Page, I. H.: The Relationship of the Extrinsic Renal Nerves to the Origin of Experimental Hypertension, *Am. J. Physiol.* **112**:166, 1935. Collins, D. A.: Hypertension from Constriction of the Arteries of Denervated Kidneys, *ibid.* **116**:616, 1936.

23. Goldblatt, H.; Gross, J., and Hanzal, R. F.: Studies on Experimental Hypertension: II. The Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, *J. Exper. Med.* **65**:233, 1937.

24. Goldblatt, H., and Wartman, W. B.: Studies on Experimental Hypertension: VI. The Effect of Section of Anterior Nerve-Root on Experimental Hypertension Due to Renal Ischemia, *J. Exper. Med.* **66**:527, 1937.

25. Freeman, N. E., and Page, I. H.: Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs, *Am. Heart J.* **14**:405, 1937.

26. Glenn, F.; Child, C. G., and Page, I. H.: The Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs, *Am. J. Physiol.* **122**:506, 1938.

of renal vasoconstriction in hypertension in human beings, as compared with a mechanical origin in animals. Since sympathectomy in hypertensive human beings does not release the vasoconstriction which, as will be shown, is more probably humoral than neurogenic in origin, this view is inadequate. On the other hand, the animal does not usually assume the erect posture, and its splanchnic visceral innervation does not therefore have the demands placed on it which confront the visceral innervation in human beings. Indeed, it is a matter of common knowledge that prolonged forced assumption of the erect posture by a normal quadruped may lead to loss of consciousness. It is therefore probable that the difference in the effect of sympathectomy observed in hypertensive human beings and in animals is in part an expression of the erect posture of man and of the lower degree of reactivity of the visceral splanchnic innervation in animals.

The decrease of arterial pressure which follows sympathectomy in hypertensive man may be, therefore, an expression of decreased venous return, which in no way alters the possible primary genetic role of the kidney in hypertension. How, then, can clinical improvement follow such operations in cases of hypertension? It has been repeatedly shown in experimentally hypertensive animals that arteriolar lesions, such as medial hypertrophy, sclerosis and necrosis, occur only in areas exposed to high arterial pressure. The kidneys of experimentally hypertensive dogs, protected from the increased arterial pressure by the metal clamp around the renal artery or by the firm scar of perinephritis, do not show arteriolar lesions of this type. Interestingly, arteriolar lesions do occur in the contralateral "normal" kidney of rats in which hypertension has been produced by interference with the circulation of one main renal artery.<sup>27</sup> Arteriolar sclerosis and necrosis therefore depend as much on high arterial pressure as on vasoconstrictor influences. Consequently, a simple reduction of arterial pressure in a case of hypertension, even one which does not alter the primary genesis of the condition, may reasonably be expected to result in arrest of some degenerative arteriolar lesions and in the repair of others. Failure to increase renal blood flow by such a procedure as sympathectomy in no way condemns the continued use and study of a method which has been shown by competent observers to result in improvement and temporary arrest of the disease in certain cases. The absence of renal hyperemia after sympathectomy merely clarifies the mechanism by which the operation is therapeutically effective.

(b). The probable humoral pathogenesis of clinical and experimental hypertension has been reviewed elsewhere;<sup>28</sup> so detailed consideration is

27. Wilson, C., and Byrom, F. B.: Renal Changes in Malignant Hypertension: Experimental Evidence, *Lancet* 1:136, 1939.

28. Page, I. H.: Newer Knowledge of Hypertension, in *Blood, Heart and Circulation*, Publication 13, American Association for the Advancement of Science,

(Footnote continued on next page)

unnecessary in this report. Briefly, the genesis of hypertension appears to depend on the liberation in systemic blood of a crystallizable pressor substance, angiotonin. Angiotonin is formed by the enzymatic interaction of renin, a protein released into blood by the kidneys of experimentally hypertensive animals and hypertensive human beings<sup>29</sup> with renin activator, a pseudoglobulin present in blood plasma. Infusion of angiotonin<sup>30</sup> increases arterial pressure and decreases renal blood flow.<sup>31</sup> The decrease in renal blood flow is predominantly the result of efferent arteriolar vasoconstriction. The action of angiotonin therefore mimics the hemodynamic changes of hypertension. Significantly, a pressor substance which has some of the characteristics of angiotonin is present in the peripheral blood of human beings suffering from hyper-

1940. Corcoran, A. C., and Page, I. H.: Arterial Hypertension: Correlation of Clinical and Experimental Observations, *J. A. M. A.* **116**:690 (Feb. 22) 1941.

29. Page, I. H.: Demonstration of the Liberation of Renin into the Blood Stream from Kidneys of Animals Made Hypertensive by Cellophane Perinephritis, *Am. J. Physiol.* **130**:22, 1940.

30. (a) Corcoran, A. C., and Page, I. H.: The Effects of Angiotonin on Renal Blood Flow and Glomerular Filtration, *Am. J. Physiol.* **130**:335, 1940. (b) Corcoran, A. C.; Kohlstaedt, K. G., and Page, I. H.: Changes of Arterial Blood Pressure and Renal Hemodynamics Induced by Injection of Angiotonin in Human Beings, *Proc. Soc. Exper. Biol. & Med.* **46**:244, 1941.

31. The effects of angiotonin on blood pressure and renal circulation are consistent with those of a substance which when administered as such acts rapidly and soon disappears but when administered by injection of renin is slowly released into the blood.<sup>30b</sup> Renin has been shown to decrease renal blood flow in an experiment reported by G. Hessel (Ueber Renin, *Klin. Wchnschr.* **17**:843, 1938). The decrease of renal blood flow due to injection of renin is usually accompanied with increased renal volume (Merrill, A.; Williams, A. H., and Harrison, T. R.: The Effects of a Pressor Substance Obtained from the Kidneys on the Renal Circulation of Rats and Dogs, *Am. J. M. Sc.* **196**:240, 1938. Friedman, B.; Abramson, O., and Marx, W.: Pressor Substance in the Cortex of the Kidney, *Am. J. Physiol.* **124**:285, 1938), which is presumptive evidence of increased glomerular volume and therefore of efferent arteriolar vasoconstriction (Richards, A. N., and Plant, O. H.: Urine Formation in the Perfused Kidney: The Influence of Adrenalin on the Volume of the Perfused Kidney, *Am. J. Physiol.* **59**:184, 1922). Slow intravenous infusions of renin have been observed to decrease renal flow and greatly increase the proportion of inulin removed (Corcoran, A. C., and Page, I. H.: The Effects of Renin, Pitressin and Pitressin and Atropine on Renal Blood Flow and Clearance, *Am. J. Physiol.* **126**:354, 1938; The Effects of Renin on Renal Blood Flow and Glomerular Filtration, *ibid.* **129**:698, 1940) from the plasma in the glomeruli. The increased extraction of inulin is unequivocal evidence of increased intraglomerular pressure. The increased intraglomerular pressure is apparently not due to the simultaneous increase of systemic arterial pressure (Corcoran, A. C., and Page, I. H.: The Effects of Renin, Pitressin and Pitressin and Atropine on Renal Blood Flow and Clearance, *Am. J. Physiol.* **126**:354, 1938) and is therefore the result of intense constriction of the glomerular efferent arterioles.

tension. The release of renin, which initiates the process, appears not to depend primarily on renal ischemia but rather on a change from pulsatile to continuous blood flow within the kidney, i. e., on intrarenal reduction of pulse pressure. Renal vasoconstriction in cases of hypertension is therefore probably secondary to the unopposed release of the renal vasopressor system and is humoral and not neurogenic in origin. From this point of view, section of renal nerves would not be expected to result in a release of the abnormal renal vasoconstriction. It should, however, be noted that sclerosis of renal arterioles, the result in part of increased arterial pressure, would probably add to the vicious circle of abnormal renal hemodynamics which maintains the release of renin from the kidneys of hypertensive patients. Interruption of the sclerotic process as a result of decreased arterial pressure after sympathectomy might well be expected to restrict, for a time at least, the further progress of the disease.

#### SUMMARY

Observations of preoperative and postoperative renal blood flow and filtration fractions in 2 cases of essential hypertension treated by extensive sympathectomy are reported. The operation did not increase renal blood flow or decrease the degree of efferent arteriolar constriction in either case. These observations are in accord with experimental data obtained from chronic experiments in animals and with other observations on the effect of renal denervation and sympathectomy in man.

It is concluded that the benefits of sympathectomy in cases of hypertension do not depend on improvement of renal circulation resulting from interruption of renal nerves. The suggestion is made that the decrease of arterial pressure which follows sympathectomy in hypertensive man is an expression of denervation of the reactive visceral splanchnic innervation, with resultant partial failure of venous return, most evident in the erect position. The decrease of venous return limits cardiac output and thus tends to decrease arterial pressure. It is further suggested that the decrease of arterial pressure is in itself an adequate explanation of the clinical improvement which may follow such an operation, since it may prevent the further spread of arteriolar lesions.

The probable relation of the renal vasopressor system to hypertension is reviewed, and it is noted that renal vasoconstriction in cases of hypertension is probably humoral rather than neurogenic in origin. The view is proposed that decreased arterial pressure occurring as a result of sympathectomy may arrest the progress of renal arteriolosclerosis in a hypertensive patient and that, since these arteriolar lesions may contribute to the release of renin and the activity of the renal vasopressor system, sympathectomy may thus interrupt for a time the progress of the disease.



# A NEW METHOD FOR PHYSIOLOGIC DECOMPRESS- SION AFTER GASTRIC OPERATIONS

## PRELIMINARY REPORT

WILLIAM RAFFEL, M.D.

BALTIMORE

Surgeons have for many years attempted decompression of the stomach after gastroenterostomy or subtotal gastric resection. This was finally accomplished with the Wangensteen suction method, and the morbidity and mortality of gastric surgical procedures were materially reduced. However, experimental work by Peters and others has shown that acid ions (chiefly chlorides), when removed from the stomach by prolonged vomiting or by continuous suction drainage, cannot be replaced by the parenteral administration of saline solution, because of the cellular depletion of acid ions with the resultant base retention and cellular edema. It was thus shown that the disrupted acid-base equilibrium can be reestablished only after prolonged oral administration of the required acid components. The continued maintenance, therefore, of the acid-base equilibrium from the time of the operation is likely to prevent to some degree the usual edema at the stoma. The obvious answer to the problem is replacement of the normal gastric secretion plus administration of a maintenance dose of salt and fluid.

Another problem which has caused no little concern is closure of the duodenal stump after subtotal gastric resection. A considerable percentage of the operative mortality following this procedure has been due to peritonitis following the blowout of the duodenal stump, which is frequently left rather short and with little serosal covering. The cause of disruption of the duodenal suture line is believed by some surgeons to be obstruction (early) at or near the stoma of the anastomosis, and large quantities of duodenal contents are found in the peritoneal cavity when this complication occurs.

Hypoproteinemia occurs rather early after gastric resection and is overcome to some degree by transfusion of either plasma or blood.

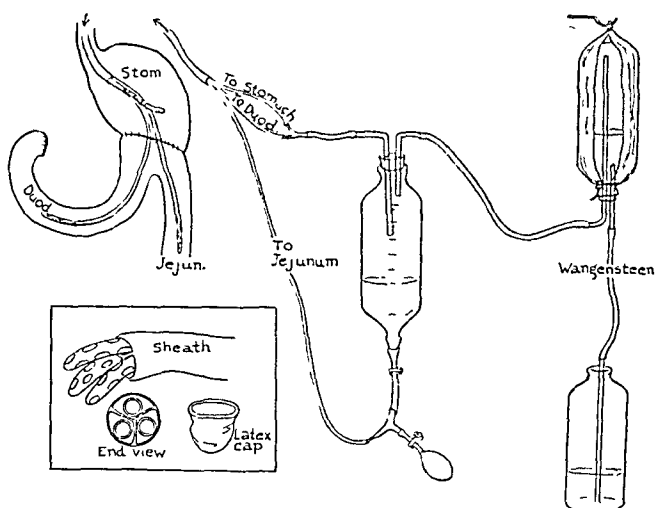
It was therefore deemed advisable to devise a method which would decompress not only the stomach but the duodenal loop. Such a procedure would be particularly advantageous if at the same time one

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From the Surgical Service of the Sinai Hospital of Baltimore.

could feed back into the normal distal jejunal loop the secretions collected from the stomach and duodenum plus such exogenous material as might be required. Tension at the suture lines would then be minimized. Cellular edema could be controlled and hypoproteinemia overcome. It was further surmised that the pancreatic enzymes, bile and gastric secretion fed into the jejunal loop could reinstitute the function of the duodenum. However, it was feared that jejunal ulcerations might occur as the result of such a process, and work dealing with that possibility is now in progress.

For the purposes mentioned a rubber tube has been devised which carries on all these functions simultaneously. The tube (see illustra-



Tube for decompression of the stomach and the duodenal loop after gastric resection.

tion) consists of a soft latex rubber sheath divided into three separate channels, each containing a soft rubber catheter of no. 8 French caliber. The catheters are freely and independently movable within the sheath, are of distinctive colors and are opaque to roentgen rays. The end of the sheath is covered with a tightly fitting latex cap to facilitate passage of the tube.

The tube is passed through the nasopharynx into the stomach on the morning of the operation. After the resection has been completed and the posterior layers of the gastrojejunostomy closed, the rubber cap is removed from the end of the sheath and the tubes distributed to (1) the stomach, (2) the proximal duodenal loop and (3) the distal jejunal loop. Tubes 1 and 2 are then attached to a negative pressure

trap with continuous Wangensteen suction, and the secretions, physiologic solution of sodium chloride and proteins in suitable form are fed to facilitate passage of the tube.

The apparatus is simply handled and easily used, and it causes no more discomfort to the patient than the ordinary Levine tube.

Patients have been intubated and the practicability of the apparatus proved. However, the work is incomplete, and controlled experiments will be reported in the near future.

# EARLY RISING AND AMBULATORY ACTIVITY AFTER OPERATION

A MEANS OF PREVENTING COMPLICATIONS

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AND

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DETROIT

Since January 1938 we have performed 383 appendectomies at St. Joseph's Mercy Hospital, Detroit. Thirteen of these appendectomies were done in cases in which the appendix was ruptured and there was spreading or generalized peritonitis, and the patients were not considered suitable for the early ambulatory treatment about to be described. The diagnoses in the remaining 370 cases were as follows: chronic appendicitis, 108 cases; mild appendicitis, 153 cases; acute appendicitis, 69 cases, and empyema or gangrene of the appendix without rupture, 40 cases (tables 1 and 2).

## RESULTS WITH THE REGIMEN IN THREE HUNDRED AND SEVENTY CASES IN WHICH APPENDECTOMY WAS PERFORMED

In this series of 370 cases the average period of confinement to bed after operation was one and a half days and the average period of hospitalization after operation two and three-tenths days (tables 1 and 2). In 2 cases Meckel's diverticulum was also removed through the appendectomy incision. Confinement to bed in each of these cases was for one day. One patient was an obese woman who was ambulatory on the first postoperative day but returned to bed on the third day with a deep wound infection for which she was treated with sulfanilamide. She was again ambulatory on the eighth day. Another patient, a 24 year old man, was ambulatory on the first postoperative day and left the hospital on the fourth day. On the sixth day he appeared at the office in excellent condition, but at 4 a.m. of the eighth day he suddenly experienced a sharp pain in the lower part of the abdomen and reentered the hospital for observation. An abscess developed at the base of the cecum, which was drained through the abdomen. After operation he performed routine exercises in bed, and on the third postoperative day he was out of bed for short periods. The exercises were gradually increased, and he left the hospital on the fifteenth postoperative day. In addition, there was

a minor wound infection in 15 cases. The patients with infected wounds were not confined to bed for treatment and came to the office for dressings. There were no other complications.

During the first twenty-four hours after operation the patients were given 2 ounces (60 cc.) of water every two hours and as much morphine as was required to relieve pain. The diet was then gradually increased.

TABLE 1—*Number of Days of Confinement to Bed After Appendectomy in Three Hundred and Seventy Consecutive Cases of Appendicitis\**

Number of Days	Number of Cases by Grade of Appendicitis †					Percentage of Total Number of Cases
	1	2	3	4	All Grades	
1.	76	120	55	26	277	74.84
2.	19	14	8	5	46	12.42
3.	8	11	2	6	29	7.83
4	3	3	3	2	11	3.0
5	1	2		1	4	1.1
6			1		1	0.27
7						
8	1	1			2	0.54
Total	108	153	69	40	370	100.00

The average number of days of confinement to bed for the 370 cases was 1.5

\* Thirteen additional cases, in which the appendix was ruptured, are excluded from this table and from table 2.

† The grades of appendicitis are as follows: 1, chronic; 2, mild, recurrent; 3, acute; and 4, gangrenous or accompanied by empyema without rupture.

TABLE 2—*Number of Days of Confinement to the Hospital After Appendectomy in Three Hundred and Seventy Consecutive Cases of Appendicitis*

Number of Days	Number of Cases by Grade of Appendicitis					Percentage of Total Number of Cases
	1	2	3	4	All Grades	
1	34	60	30	13	137	37.0
2	38	50	19	11	118	31.9
3	15	20	10	7	52	14.05
4	12	12	7	6	37	10.0
5	4	6	1	2	13	3.5
6	2	5	1		8	2.2
7	1		1		2	0.54
8	1				1	0.27
9						
10				1	1	0.27
11	1				1	0.27
Total	108	153	69	40	370	100.00

The average stay in the hospital after appendectomy for the 370 cases was 2.3 days

Enemas and cathartics were not given, but liquid petrolatum was usually prescribed on the third or fourth day.

After operation the patients were turned frequently in bed and were instructed to be active and to take deep breathing exercises at regular intervals. On the first postoperative day, provided conditions were satisfactory, they were assisted in sitting on the edge of the bed (after assuming the right lateral position) and then in standing beside the bed for deep breathing exercises. (This consumed only a few moments.) While in

each position they were instructed to take several deep inhalations and were urged to cough. This procedure seldom failed promptly to clear the lungs of accumulations of mucus. After this was accomplished they were permitted to walk about the room and to sit in a chair for a few moments, and then they returned to bed. On returning they sat on the edge of the bed and reclined on the right shoulder. These sitting-up and ambulatory exercises were always first carried out under the supervision of one of us. Such exercises were then repeated during the first post-operative day with the assistance of a nurse, and thereafter the patients were encouraged to increase their activities voluntarily. They left the hospital by automobile and routinely presented themselves at the office for the first dressing on the sixth postoperative day. Rarely was it necessary to see the patients in their homes. However, on dismissal from the hospital instructions were given to communicate with us by telephone the following day. A vast majority of the patients, selected on the basis of their mental attitude and general well-being, were permitted to do light work on the eighth day and to undertake heavy manual labor on the fourteenth day.

#### RESULTS WITH THE REGIMEN IN SIXTY-SIX CASES IN WHICH OTHER OPERATIONS WERE PERFORMED

We were so impressed by the rapid recovery and the freedom from complications in the cases in which appendectomy was performed that we were induced to apply this method of postoperative care after other operations, and more recently we have used it with all types of major surgical procedures. The results after these operations were also gratifying.

In a series of 66 cases the average period of confinement to bed after operation was one and nine-tenths days and the average period of post-operative hospitalization eight and nine-tenths days (table 3). In computing these averages we included the periods for 3 patients who underwent cholecystotomy for obstructive jaundice, marsupialization of a pancreatic cyst and cholecystotomy for biliary cirrhosis; these patients were hospitalized for twenty-one, thirty and thirty days, respectively. There were no complications in these cases, but the patients chose to remain in the hospital because of drainage.

In 1 case an exploratory operation was performed because of sudden severe abdominal pain and boardlike abdomen (probable diagnosis, perforated duodenal ulcer). No pathologic condition was found. The patient was confined to bed for one day.

In another case a Devine antral exclusion operation was performed for massive hemorrhages from a gastrojejunal ulcer. The patient was in a critical condition on admission and was still a poor operative risk

after three weeks of preparation. After operation his condition was unsatisfactory. However, deep breathing and special exercises of the voluntary muscles were employed during his confinement to bed. On the second postoperative day he sat on the edge of the bed; he stood beside the bed on the third day and was ambulatory on the fourth day and thereafter. He had a normal bowel movement on the seventh day and left the hospital on the eleventh day in good condition. Three days later he experienced a severe pain in the epigastrium and was rehos-

TABLE 3.—*Number of Days of Confinement to Bed and to the Hospital After Operation in Sixty-Six Cases*

Operation	Number of Cases	Average Number of Days After Operation Spent	
		In Bed	In Hospital
Celiotomy (for bleeding jejunal ulcer)*.....	1	1.0	7.0
Cholecystectomy † .....	18	1.5	8.3
Cholecystotomy ‡ .....	2	2.0	26.0
Devine operation (for bleeding jejunal ulcer)*.....	1	2.0	11.0
Excision of retroperitoneal gland (carcinoma).....	1	1.0	6.0
Exploratory laparotomy .....	1	1.0	6.0
Gastrectomy .....	1	1.0	11.0
Gastroenterostomy .....	2	1.5	9.5
Herniorrhaphy § .....	9	1.8	6.5
Marsupialization of pancreatic cyst.....	1	5.0	30.0
Nephrectomy .....	1	4.0	9.0
Pelvic operations:			
Hysterectomy .....	7	2.4	8.1
Oophorectomy, unilateral ¶ .....	2	3.0	12.0
Salpingectomy, bilateral .....	1	9.0	11.0
Other procedures .....	6	1.0	6.7
Prostatectomy .....	1	2.0	18.0
Removal of adhesions (intestinal obstruction).....	2	1.0	9.5
Splenectomy .....	2	2.0	8.5
Thyroidectomy ¶ .....	7	1.9	6.0
Total.....	66		

For the total of 66 cases the average time after operation spent in bed was 1.9 days and in the hospital was 8.9 days.

\* Both operations were performed on the same patient, who died. He underwent the Devine operation on Dec. 3, 1940 and celiotomy on Jan. 2, 1941.

† Gallstones were present in 14 cases, in 2 of which the gallbladder was gangrenous.

‡ In 1 case there was biliary cirrhosis.

§ There was a direct inguinal hernia in 2 cases, in 1 of which an operation for perineal repair was performed and in the other appendectomy, in addition to herniorrhaphy.

¶ In 1 case there was a large ovarian abscess.

¶ In 1 case the patient had diabetes and partial heart block.

pitalized. Roentgen examination revealed a gastrojejunal ulcer at the new outlet. Several days later he had a severe gastric hemorrhage and was operated on again. A new ulcer had perforated at the gastrojejunal junction but was walled off. This site was entered during the exploration. The patient went into severe shock, and his condition did not permit further operative procedures. A catheter was placed in the jejunum through the perforation and the abdomen closed. The usual emergency measures were employed and were followed later by deep breathing exercises and special exercises of the voluntary muscles. By the first postoperative day the patient was able to sit on the edge of the

bed, and for a short period on each day thereafter he stood beside the bed for deep breathing exercises. During the seventh night after operation he had another severe gastric hemorrhage, and he died the following day. Postmortem examination revealed "multiple ulcers of the jejunum at the point of second gastrojejunal anastomosis, probably due to a blood dyscrasia."

The postoperative treatment in this series of cases was much the same as that used after the appendectomies except that for the sicker patients periodic rhythmic contractions of the voluntary muscles were also employed at regular intervals and that the exercises out of bed (standing beside the bed for deep breathing and the beginning of ambulatory activity) proceeded somewhat more slowly and usually were performed only once daily for the first day or two under the supervision of one of us.

Improvement was usually rapid with this method of management. Wangenstein suction was instituted in from one to several days after operation in the cases in which more serious operations on the upper part of the abdomen and the pelvis were performed. Small enemas were given only occasionally and then only when rectal examination revealed that they were necessary. Transfusions, parenteral administration of fluids and chemotherapy were also employed when indicated. Many of the patients appeared at the office for removal of skin retention sutures on the tenth or the eleventh day after operation. Many patients were permitted to do light work on the twenty-first postoperative day. There were no wound infections in this series.

#### COMMENT

For all appendectomies a muscle-splitting incision was used, and the wound was closed with single, no. 0 chromic catgut. In all operations on the gallbladder an oblique incision below the costal arch, bordering on the transverse, which severed all structures, was employed. All abdominal incisions were closed with continuous, double, no. 0 chromic catgut for the peritoneum and the posterior fascia, and one or more interrupted buried sutures of steel wire, with a continuous suture of double, no. 0 chromic catgut, were used for the anterior sheath. The suture of steel wire consists of a double loop, the first loop including the fascia about one-half inch (1.3 cm.) from the edge and the second approximating the edges before ligation.<sup>1</sup> In some of our more recent cases interrupted double loop sutures of nylon were employed. All abdominal operations were performed with the patient under spinal anesthesia.

We have seen no untoward effects from this method of management and are convinced that the morbidity, the number of complications and

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1. Jones, T. E.: Personal communication to the authors.



the period of disability have been materially reduced because of the exercises in bed, the early rising and the ambulatory activity.

Since there were no pulmonary or vascular complications (except hemorrhage) in the entire series, our clinical results suggest the possibility that certain pathologic reflexes<sup>2</sup> originating from the area of mechanical and chemical injury impair respiration and initiate a delay in peripheral circulation, which leads to complications, and that strict confinement to bed favors the development of such complications. The following effects are produced by the pathologic reflexes and the recumbent position:

1. There is a limited excursion of the thoracic cage, which delays the capillary circulation in the lungs and the return flow in the vena cava and the portal system and also favors the accumulation and the retention of bronchial secretion. McMichael and McGibbon,<sup>3</sup> on the basis of their work on respiration at the Royal Infirmary, Edinburgh, estimated that in the recumbent position the total volume of air in the lung is decreased by 340 cc. on the average and the total volume of blood in the pulmonary vessels is materially increased. Khromov<sup>2a</sup> reported that those of his patients who were confined to bed for four to six days after appendectomy had a temporary reduction in vital capacity of from 36 to 48 per cent.

2. Vasospasm and capillary dilatation are produced, which results in sluggish peripheral circulation. Ochsner and DeBakey<sup>2d</sup> have demonstrated by means of plethysmographic tracings that vasospasm is present in cases of thrombophlebitis and that it can be relieved by infiltration of the paravertebral ganglions with procaine hydrochloride.

If these conditions are prolonged and the delay in circulation reaches the point of anoxia, impairment of cellular metabolism may occur. One can readily appreciate how this would favor the development of complications.

Many surgeons are conscious of the importance of stimulating the circulation after surgical procedures and advocate gymnastics and deep

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2. (a) Khromov, B. M.: Value of Early Rising After Operation in Prevention of Postoperative Pulmonary Complications, *Sovet. khir.*, 1936, no. 9, p. 389. (b) Kuntz, A.: *The Autonomic Nervous System*, ed. 2, Philadelphia, Lea & Febiger, 1934, p. 476. (c) Ranson, S. W.: *Anatomy of the Nervous System*, ed. 4, Philadelphia, W. B. Saunders Company, 1931, p. 342. (d) Ochsner, A., and DeBakey, M.: The Rational Consideration of Peripheral Vascular Disease Based on Physiologic Principles, *J. A. M. A.* **112**:230 (Jan. 21) 1939; Thrombophlebitis: Role of Vasospasm in the Production of Clinical Manifestations, *ibid.* **114**:117 (Jan. 13) 1940; Treatment of Thrombophlebitis by Novocaine Block of Sympathetics, *Surgery* **5**:491 (April) 1939.

3. McMichael, J., and McGibbon, J. P.: Postural Changes in Lung Volume, *Clin. Sc.* **4**:175 (Dec.) 1939.

breathing exercises in bed.<sup>4</sup> Many of the patients of Mermingas<sup>5</sup> who underwent appendectomy were ambulatory on the day of the operation. Mukhina<sup>6</sup> reported 527 cases of appendicitis in which operation was performed during the acute stage of the disease; in 59 per cent the patient was ambulatory on the first day, in 23 per cent on the second day, in 8 per cent on the third day and in the remaining 10 per cent shortly afterward. There were pulmonary complications in 13 cases and minor complications in a few others but no deaths. Kimbarovsky<sup>7</sup> reduced the incidence of pulmonary complications following gynecologic operations from 4.49 to 0.79 per cent, and the incidence of complications following gastric operations from 12.5 to 0.66 per cent, by getting the patients out of bed soon after operation.

When are early rising and ambulatory activity contraindicated, and when should these measures be instituted? Early rising and ambulatory activity after surgical operations on the abdomen are contraindicated if the pathologic reflexes are too pronounced, that is, if there is undue rigidity of the abdomen, undue intestinal distention or severe shock. During the period immediately after operation change of position, deep breathing exercises and periodic rhythmic contractions of voluntary muscles are employed. Paralytic ileus and severe shock as a rule occur early, usually within twenty-four hours after the operation. It is usually after this twenty-four hour period that atelectasis, pneumonia, thrombophlebitis, embolism and the detrimental effects of anoxia and toxic retention in the vital organs occur; it is during the intermediate period that early rising and graduated ambulatory activity should be instituted. The patient may be ambulatory with a Wangenstein tube in position. No patient should ever be ambulatory who has marked abdominal distention or an insecure wound.

#### CONCLUSIONS

In a large percentage of cases prolonged confinement to bed after operation may be conducive to complications. In the cases reported the patients who were active on the first postoperative day had the most favorable convalescences. No dehiscence, hernia, pneumonia, thrombophlebitis or other serious complications (except 1 instance of fatal hemorrhage) occurred in the entire series of 436 cases in which early rising and ambulatory activity were employed.

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4. Pool, E. H.: Systematic Exercise in Postoperative Treatment, *J. A. M. A.* **60**:1202 (April 19) 1913.

5. Mermingas, K.: Die Appendektomie ohne folgende Muskelnahrt, *Zentralbl. f. Chir.* **60**:553 (March 11) 1933.

6. Mukhina, M. V.: Early Rising After Appendectomy in Acute Period, *Vestnik khir.* **40**:231, 1935.

7. Kimbarovsky, cited by Khromov.<sup>2a</sup>

Our records show that this method of postoperative management is a safe procedure. It decreases atrophy from disuse of the sutured layers and may promote healing by improving the circulation in the area of the wound. Early rising and graduated ambulatory activity, instituted at the opportune time, constitute an effective method of decreasing morbidity and complications by increasing the rate and the depth of breathing and by increasing the tone and the use of the skeletal muscles, thus improving the circulation in the pulmonary, systemic, portal and lymphatic systems. It probably promotes the return of normal function of the vital organs and aids elimination through the kidneys. It shortens the period of disability, which is a monetary saving, although this has not been a factor in determining our course of treatment.

# CARCINOMA OF THE CYSTIC DUCT

REPORT OF A CASE AND COMMENTS ON LIGATION OF THE  
HEPATIC ARTERY IN MAN

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AND

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Carcinoma of the cystic duct is rare. Stewart, Lieber and Morgan,<sup>1</sup> in a critical review of the 27 cases which they found reported in the literature, divided them into four groups: 1. Those in which there appeared to be also gross involvement of the gallbladder. 2. Those in which histologic study of the neoplasm in the cystic duct and gallbladder was lacking. 3. Those in which histologic study of the gallbladder was lacking. 4. "A case of small localized polypoid tumor of the cystic duct, together with metastases in the liver, abdominal lymph nodes, in Virchow's node, and the rectal wall. The tumor in the cystic duct was diagnosed histologically as carcinoma solidum. The gallbladder was not described, and the rectum was insufficiently considered as a possible primary source for the growth." These authors in conclusion stated: "We are therefore unable to consider any of these cases as indisputable instances of primary carcinoma of the cystic duct. Obviously extreme care must be taken to exclude cancer of the gallbladder, pancreas, stomach, duodenum and rectum in order to substantiate the case."

The purpose of this report is to record what appears to be an instance of primary carcinoma of the cystic duct, together with the experiences in attempting to remove it.

## REPORT OF CASE

A white man aged 63 was admitted to the medical service Oct. 6, 1940, complaining of "soreness and heaviness in the stomach," icterus and generalized pruritus of three weeks' duration. His usual weight was stated to be 190 pounds (86 Kg.), but on his admission to this hospital his weight was 169 pounds (76.7 Kg.). General physical examination gave essentially negative results except for generalized moderately severe icteric discoloration. The leukocyte count was 9,000 and the erythrocyte count 4,530,000 per cubic millimeter of blood; the icteric

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From the Departments of Surgery and Medicine, the University of Chicago.

1. Stewart, H. L.; Lieber, M. M., and Morgan, D. R.: Carcinoma of the Extrahepatic Bile Ducts, Arch. Surg. **41**:662 (Aug.) 1940.

index was 115. The blood pressure was 110 systolic and 65 diastolic. The pulse rate was 72. The temperature was normal. The Wassermann and Kahn reactions were negative. Roentgenograms of the chest revealed no abnormality. There was no evidence of calcified stone in the gallbladder.

The clinical impression was carcinoma of the head of the pancreas (or of the ampulla of Vater).

*Laparotomy (October 8).*—Procaine hydrochloride spinal, ethylene and ether anesthesia was used. The abdomen was entered through a high midline incision. Exploration revealed nothing abnormal except a very hard rounded mass in the region of the confluence of the cystic and hepatic ducts. This mass was about 3 cm. in diameter and was surrounded by fibrous adhesions. The head of the pancreas felt normal. The confluence of the hepatic ducts above the mass was considerably dilated, whereas below the mass the common duct was almost of normal size. The gallbladder was not markedly distended; its wall was slightly thickened, and a few small gallstones were palpated within it. It was possible to ascertain that the mass was not closely adherent to the portal vein, and resection of the mass, together with the gallbladder, was accomplished by transection through the con-

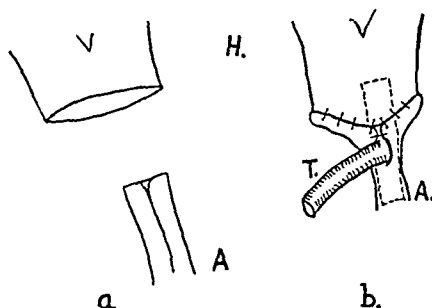


Fig. 1.—Diagrammatic illustration of the method employed in anastomosis of the hepatic duct and the lower segment of the common duct after resection of the gallbladder, cystic duct, carcinoma and a segment of the hepatic artery.

Prior to anastomosis (a) there was a marked difference in size between the confluence of the hepatic ducts (H) and the lower segment of the common duct (A). A slit was made on the anterior aspect of the latter.

Anastomosis (b) between the hepatic ducts and the common duct was performed with interrupted silk sutures. The long arm (T) of the T tube was brought out through the lower angle of the split in the wall of the common duct and is thus away from the main line of the anastomosis. The split also facilitates accommodation of the smaller common duct orifice to the larger confluence of the hepatic ducts.

fluence of the hepatic ducts above and the common duct below. During this step it became evident that a segment of hepatic artery had been removed, since this artery coursed through the tumor. Ligation was performed at the limits of resection. A longitudinal slit was made in the common duct to accommodate the stem of a T tube, one arm of which extended upward into the hepatic duct and the other into the common duct (fig. 1). Anastomosis was accomplished by a circular series of interrupted black silk sutures. The abdomen was closed with a cigaret drain placed into the right renal fossa. A silk technic was used throughout.

*Surgical Pathologic Study.*—The specimen consisted of a normal-sized gallbladder with slightly thickened walls. When opened it contained about 10 cc. of very thick, pale green mucoid secretion and several small pigmented gallstones. The mucosal surface was smooth, intact and covered with flakes of soft greenish and reddish material. The neck of the gallbladder appeared to arise from a rounded tumor mass 3.2 cm. in diameter, which had replaced the cystic duct (*A*, fig. 2) and whose surface was roughened by cut fibrous adhesions. At what

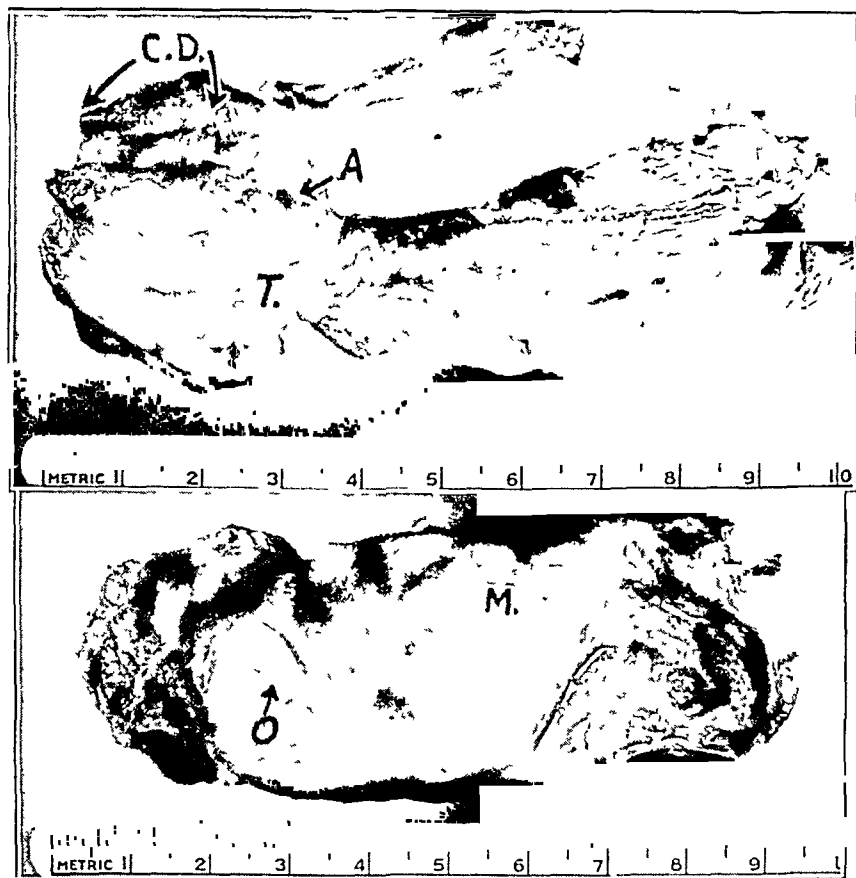


Fig. 2.—Above, surgical specimen of the gallbladder. Note the tumor mass (*T*) involving the cystic duct and the excised segment of the common duct, *CD*. The opened gallbladder is seen from the serosal aspect; the cut edges are rolled upward. An incision has been made into the tumor mass, showing yellow-gray mottled surfaces. *A*, patent orifice of the excised segment of the hepatic artery. Below, surgical specimen seen from the opposite aspect. *M*, mucosal surface of gallbladder; *O*, proximal orifice of the cystic duct tightly dilated by yellow-gray tumor mass arising in the cystic duct and pressing backward toward the lumen of the gallbladder.

appeared to be the junction of the gallbladder with what had been the cystic duct there was a rounded, tightly stretched rim of mucosa over a firm grayish yellow mass bulging backward toward the gallbladder (*B*, fig. 2). The appearance was

that of a mass that had filled completely the cystic duct and was expanding backward in its lumen. The tip of a probe could be inserted between the stretched rim of the mucosa and the tumor mass, elevating the former off the latter. Over the opposite aspect of the mass, i. e., away from the gallbladder, there was a segment of common bile duct 3 cm. in length (*A*, fig. 2). Most of the circumference of this duct was closely adherent to the tumor mass and could not be easily peeled away from it. The mucosa appeared intact and normal. The entrance of the cystic duct was readily identified but could be followed for only about 3 mm. before the finely granular gray-yellow surface of the tumor mass was encountered completely filling the lumen; at this point the identity of the cystic duct was lost. Almost in the center of the tumor mass and coursing parallel to the segment of the common duct was a segment of artery identified as the hepatic artery. The walls were closely adherent to the surrounding tumor

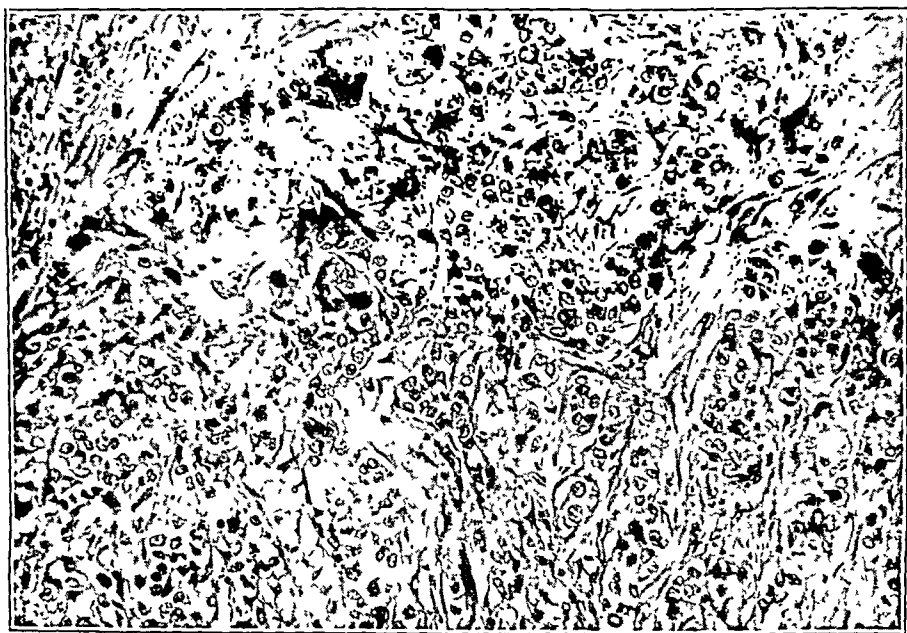


Fig. 3.—Photomicrograph of a carcinoma of the cystic duct, showing marked anaplasia and two types of cells, those with granular cytoplasm and the so-called clear cells.

tissue. Incision into the tumor mass failed to reveal gross structures suggesting remnants of the cystic duct. Indeed, the latter seemed to have been completely replaced. Multiple yellowish pockets of soft degenerated tissue were present throughout the mass.

Microscopic study of sections of the tumor showed it to be composed of irregular masses and cords of rather large polyhedral and square cells with moderate-sized vesicular nuclei. Two types of tumor cells were readily identified (fig. 3)—cells with finely granular cytoplasm and cells with cytoplasm which appeared practically clear (clear cell type of carcinoma). Occasionally both types of cells exhibited an arrangement which suggested acinar or alveolar formation. Many scattered areas of necrosis with leukocytic infiltration were present. Section through the walls of the common bile duct and the hepatic artery showed

infiltration of the serosal layers by nests of tumor cells. Sections through the wall of the gallbladder showed serosal thickening and slight diffuse leukocytic infiltration of all layers of the wall. The mucosa was intact. No tumor cells were observed in the sections of gallbladder wall studied.

The surgical pathologic diagnosis was carcinoma of the cystic duct, with infiltration about the common bile duct and the hepatic artery.

*Course.*—The immediate postoperative course was satisfactory. The maximum temperature was 99.6 F. and was noted on the second day. The temperature was normal thereafter. Drainage from the T tube varied from 300 to 1,000 cc. of bile per day; it was more often closer to the latter figure. The icterus, however, increased for three days, the icteric index being 200 on the third postoperative day. The appetite rapidly returned, and by the seventh day the patient was eating well of a soft diet. There was no abdominal distention. On the tenth day there was profuse biliary drainage about the T tube as well as through it. The patient complained of epigastric pain and vomited between 1,000 and 2,000 cc. of bile-stained fluid containing undigested food. There was no abdominal distention or rigidity. By the fourteenth day satisfactory convalescence was apparently continuing. On the fifteenth day vomiting recurred. By the nineteenth day most of the bile was being discharged about the T tube. The tube was therefore removed (it came away easily). All skin sutures also were removed. The leukocyte count was 13,600 and the erythrocyte count 4,400,000 per cubic millimeter of blood. On the twentieth day there was discomfort in the upper part of the abdomen and the patient exhibited a drawn expression. On the twenty-first day he vomited several times. The icteric index was 62, the lowest since admission. On the evening of the twenty-second day administration of a 10 per cent solution of casein digest (amino acids) intravenously was started, and during the subsequent hour and a half 200 cc. was given; at about 10 p. m., there was a moderately severe chill, and the intravenous injection was then discontinued, after which all discomfort disappeared. However, the patient died suddenly about one and a half hours later. There had been no recurrence of untoward symptoms.

The values for plasma protein were as follows: day before operation, 6.59 Gm. per hundred cubic centimeters; fourth postoperative day, 5.91 Gm.; sixth postoperative day (two days before death), 4.1 Gm.

Necropsy was performed in the department of pathology of the University of Chicago Clinics. The salient gross features were: 1. There was no peritonitis. 2. On the anterior margin of the right lobe of the liver there was a sharply demarcated, wedge-shaped area of infarction with the apex toward the hilus, measuring 8 cm. in its greatest diameter; a similar area, 3 cm. in diameter, was seen at the posterior midmargin of the right lobe. There were no metastases. 3. The anastomosis of the extrahepatic bile ducts was intact except at the point of exit of the previously inserted T tube. 4. The pancreas was normal. 5. Eight millimeters below the pylorus there was a sharply outlined acute duodenal ulcer measuring 8 by 4 mm. There was no evidence of hemorrhage from this.

The salient histologic observations were: 1. There were moderate chronic passive congestion of the liver and some bile canaliculi distended with bile. There was slight diffuse lymphocytic infiltration. No fatty degeneration or infiltration was observed. There was beginning organization of the infarcts about their peripheries. The appearance of the infarcted areas was characteristic; i. e., there was massive coagulation necrosis with preservation of cell "shadows." 2. No definite metastases to lymph glands were seen, but small nests of tumor cells were present in the fibrous tissue about the resected portions of the bile ducts. 3. The duodenal ulcer had eroded to the muscularis.



## COMMENT

The exact cause of death in this instance is not clear, though it is suggested that there was ultimate hepatic failure of some type, in view of the very rapid fall in the level of plasma proteins from 5.91 to 6.18 Gm. per hundred cubic centimeters on the fourth and sixth post-operative days to 4.1 Gm. twelve days later, two days before death. This could hardly be accounted for on a dietary basis. The failure of the liver must certainly have been the result of resection of the hepatic artery, which procedure was the direct cause of the infarcts. It would appear, however, that some degree of recovery from the latter occurred, since the patient survived the operation for twenty-two days and organization of the infarcts had begun. Further evidence that the liver functioned to some extent for a time at least is afforded by the fact that on the day before operation the value for prothrombin was 46 per cent; on the day of operation (vitamin K had been administered, and this was continued daily for a time) it rose to 86 per cent; on the sixth day it was 82 per cent, and it reached 100 per cent on the ninth day, after which no more of the vitamin was given. Unfortunately no prothrombin determinations were made subsequently. The reaction to the injection of the casein digest is not considered by the writers as the principal cause of death, since apparent complete recovery from the effects of this had occurred prior to death.

Survival after ligation in stages of the principal hepatic arteries in experimental animals has been reported by a number of investigators (see review by Huggins and Post,<sup>2</sup> with reports of their own experiments). Alessandri<sup>3</sup> in 1937 was able to collect from the literature 10 instances of ligation of the hepatic artery in man. In 6 the result was fatal, and in 4 there was recovery. It is of course probable that complete or partial ligation of the hepatic artery has been followed by recovery more often than the number of case reports would indicate, since it could take place inadvertently and without the actual knowledge of the operator. Alessandri also reviewed the 18 case reports of ligation of one of the principal branches of the hepatic artery. There were 7 instances of immediate fatality, with necrosis of the corresponding lobe, and 11 instances of recovery.

It would appear that in man recovery from ligation of the hepatic artery or one of its principal branches depends on the extent of collateral arterial circulation present in the particular patient, which in turn

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2. Huggins, C., and Post, J.: Experimental Subtotal Ligation of the Arteries Supplying the Liver, *Arch. Surg.* 35:878 (Nov.) 1937.

3. Alessandri, R.: Aneurysm of Hepatic Artery, in Nelson New Loose-Leaf Surgery, New York, Thomas Nelson & Sons, 1937, vol. 5, chap. 10-A, p. 608A.

depends on the presence or absence of accessory or otherwise adequate "anomalous" branches. Such anomalies are apparently common, and Alessandri cited the gross anatomic investigations of Tandler:

. . . to indicate their presence in 32 per cent of patients. The anomalies which so styled if present would tend to permit survival following ligation of the hepatic artery or one of its principal branches include the origin of an accessory hepatic artery from the superior mesenteric, inferior mesenteric, right suprarenal, spermatic, right renal and from the aorta itself. Rabinovitsch (cited by Alessandri), investigating the arterial blood supply of the liver in 66 cadavers found the hepatic-coronary in 28 per cent of the cases and the hepatic-mesenteric in 18 per cent. "In other words this condition of the existence of an accessory vessel occurs in 46 per cent, i. e. almost half of the cases."

#### SUMMARY

A case of carcinoma of the cystic duct is reported. Removal of the tumor entailed resection of a segment of the common duct and the main hepatic artery. Death ensued in twenty-two days after operation and was attributed to failure of the liver incident to interruption of the hepatic artery.

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